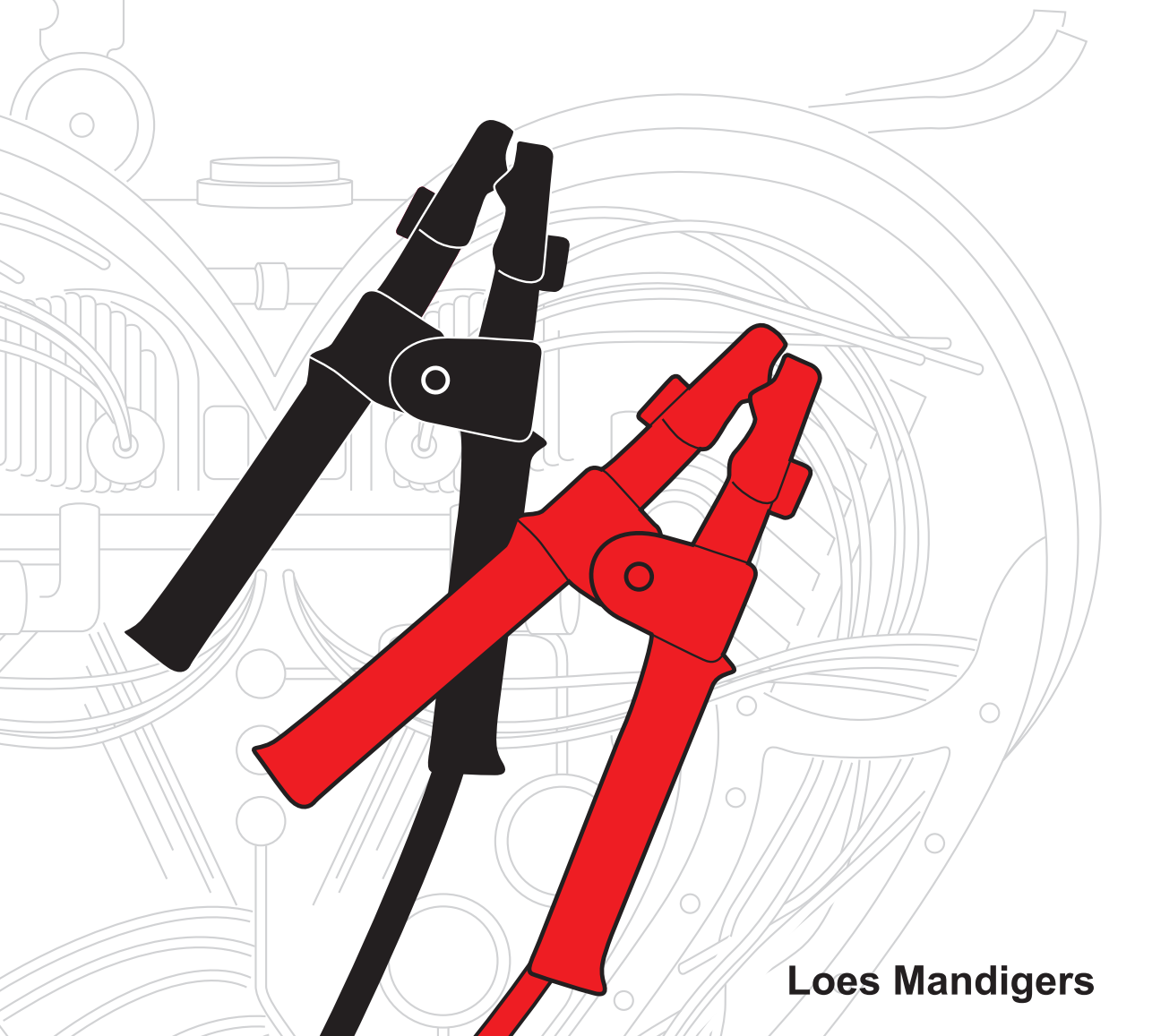
Different aspects of cardiac arrest and its treatment with extracorporeal cardiopulmonary resuscitation.



Loes Mandigers

Different Aspects of Cardiac Arrest and its Treatment with Extracorporeal Cardiopulmonary Resuscitation

Loes Mandigers

ISBN: 978-94-6361-744-4

Cover: Jan Peeters | Peeters graphics
Layout: Optima Grafische Communicatie (www.ogc.nl)
Printing: Optima Grafische Communicatie (www.ogc.nl)

Different Aspects of Cardiac Arrest and its Treatment with Extracorporeal Cardiopulmonary Resuscitation

Verschillende aspecten van hartstilstand en de behandeling met extracorporale cardiopulmonale resuscitatie

Thesis to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.

The public defence shall be held on
wednesday 19 October 2022 at 10.30 hrs

By Loes Mandigers

born in Valkenswaard

Erasmus University Rotterdam

Doctoral Committee:

Promotor:	Prof.dr. D.A.M.P.J. Gommers
Other members:	Prof.dr. J. Horn
	Prof.dr. N.M.D.A. van Mieghem
	Prof.dr. F. Zijlstra
Copromotors:	Dr. D. dos Reis Miranda
	Dr. C.A. den Uil

Financial support by the Dutch Heart Foundation for publication of this thesis is gratefully acknowledged.
We also want to acknowledge Daphne Visser-Lees for translating Chapter 1.

TABLE OF CONTENTS

Chapter 1

Introduction

Loes Mandigers, Corstiaan A. den Uil, Dinis dos Reis Miranda

Partly published in Dutch; A&I 2019 Dec; Volume 11, Edition 4

INTRODUCTION

Part of this paper has previously been published in Dutch: *Extracorporale Cardiopulmonale Resuscitatie*, A&I 2019 December, Volume 11, Edition 4

Throughout the world, the resuscitation procedure is associated with a low survival rate and the risk of a poor neurological outcome. Methods of improving the chance of survival with a good neurological outcome have been sought for many years. One of the relatively new developments in this area is the implementation of extracorporeal cardiopulmonary resuscitation (ECPR).

CONVENTIONAL CARDIOPULMONARY RESUSCITATION

Incidence and outcomes

In the Netherlands, every week 300 people suffer an out-of-hospital cardiac arrest (OHCA), which amounts to 97.5 events per 100,000 inhabitants each year. (1) No national incidence data on the number of in-hospital cardiac arrests (IHCA) are available. In other developed countries, an incidence of 1-4 per thousand hospital admissions is reported. (2, 3) Of all the resuscitation procedures in the Netherlands (both OHCA and IHCA), more than 4000 patients are admitted to an Intensive Care Unit (ICU). (4)

In the Netherlands, the percentage of hospital survivals in OHCA patients rose from 16.3% in 2006 to 20.9% in 2012. (5) In a large European study, Grasner et al (6) describe a hospital survival of OHCA patients of 1.1-30.8%. If all causes of OHCA are taken into account, then this percentage is highest in Switzerland, however, if the Utstein criteria are selected then this is the highest in the Netherlands. (6) A large meta-analysis has shown that the hospital survival percentages in IHCA patients vary between 6.0-40.0%. (7) The improvement of hospital survival in OHCA patients seen over recent years is most probably due to the training of laypeople in the recognition of circulatory arrest and to bystanders starting the resuscitation procedure (basic life support [BLS]). Another factor is the rising use of automatic external defibrillators (AEDs). (5) The number of patients admitted to hospital following an OHCA between 2006 and 2012 did not change much. In their study, Blom et al (5) reported that in 2006, 313 OHCA patients were admitted to hospital, and in 2012 this number was 335. This encompassed 36.8% and 38.3%, respectively, of the total number of OHCA patients. (5) This rise in survival is also reflected in the number of OHCA patients who are admitted to an ICU, where mortality among IHCA patients has remained stable over the years. (4) This all appears to indicate that those OHCA patients who are admitted to hospital are in a better condition due to rapid intervention.

Pathophysiology

During circulatory arrest and resuscitation, oxygen transport is limited and ischaemic injury results. However, even after the return of spontaneous circulation (ROSC), the patient continues to be at risk of injury. One of the main reasons for poor survival and neurologically unfavourable survival following resuscitation, is ischaemia and reperfusion damage. Post-anoxic brain damage is the primary cause of death in 23% of the OHCA and 68% of the IHCA patients. (8) This damage can be divided into primary injury, which occurs during circulatory arrest, and secondary injury, which occurs during the reperfusion phase.

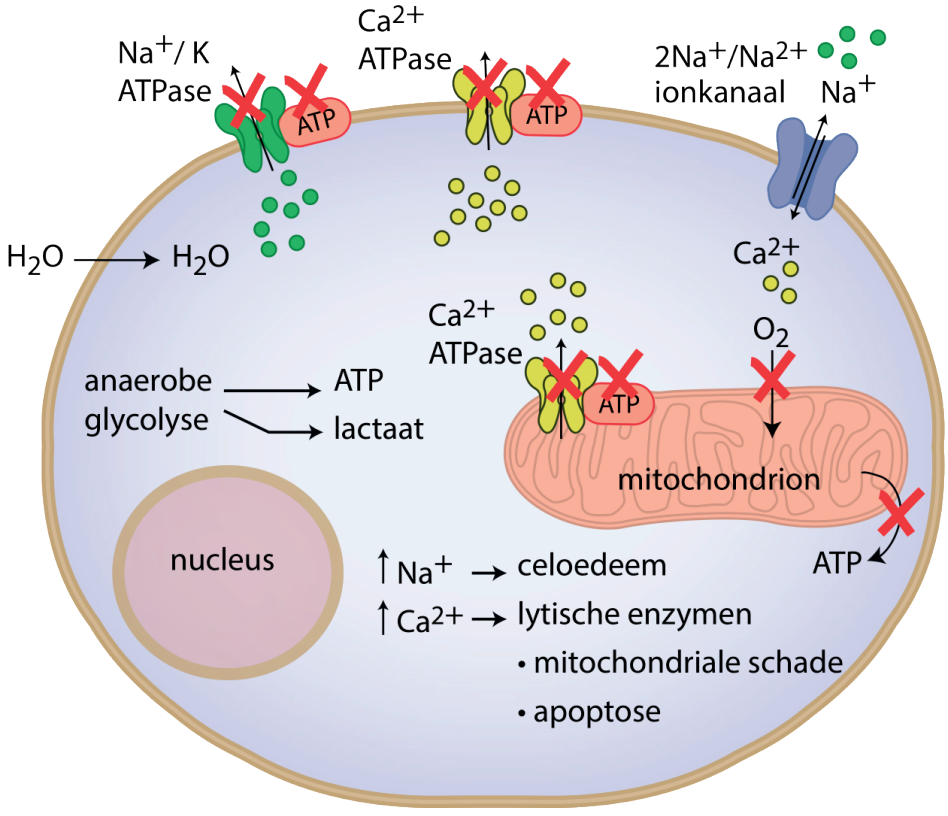


Figure 1 | Pathophysiology of primary cerebral injury due to cardiac arrest
Reduced or no oxygen supply causes the ATP to drop, triggering Na+ and Ca2+ accumulation in the cell. This results in cell oedema and the production of lytic enzymes which lead to mitochondrial damage and apoptosis. Anaerobic glycolysis causes a small amount of ATP to be produced which is accompanied by lactate production.
ATP = adenosine triphosphate, Na^+ = sodium, Ca^{2+} = calcium, H_2O = water

Primary injury

During a circulatory arrest, the loss of cerebral oxygen transport results in neuronal ischaemia and cell death within a few minutes. As shown in Fig. 1, a disruption of cerebral oxygen transport results in a reduction in the production of adenosine triphosphate (ATP) causing the energy-dependent ion channel function to stop. The intracellular sodium is then unable to leave the cell and causes cytotoxic oedema. At the same time calcium (Ca^{2+}) accumulates in the cell which causes activation of lytic enzymes and mitochondrial dysfunction, causing ATP production to further decrease. The disappearance of ATP sets the anaerobic metabolism in motion, lactate accumulates in the cerebrum, and intracellular acidosis develops. This all ultimately leads to cell apoptosis. (8)

Secondary injury

In the reperfusion phase after circulation has resumed, there are a number of processes that could cause secondary injury: hypo- and hypercapnia, hypoxaemia, failing cerebral autoregulation, cerebral vasoconstriction, reduced effectivity of the blood-brain barrier and cerebral oedema.

Carbon dioxide (CO_2):

If blood CO_2 falls below normal levels, i.e. hypocapnia, vasoconstriction develops which causes a decrease in cerebral blood flow and a decrease in intracranial pressure due to a reduction in cerebrovascular volume. This results in ischaemia. A large Dutch ICU database study carried out by Helmerhorst et al (9) shows a negative association between hypocapnia and hospital survival in OHCA patients (odds ratio [OR] 1.39, 95% confidence interval [95% CI] 1.18-1.63). In the study of Schneider et al (10), a borderline significant higher mortality was seen in hypocapnia versus normocapnia in both OHCA and IHCA patients (OR 1.12, 95%CI 1.00-1.24), and a significantly lower percentage of survival to hospital discharge in patients with hypocapnia than in those with normocapnia (OR 0.81, 95%CI 0.70-0.94). However, neither of these studies corrected for cardiac factors. (9, 10) Roberts et al (11) did correct for these factors and they also found an association between hypocapnia and poor neurological outcome in OHCA and IHCA patients (OR 2.43, 95%CI 1.04-5.68).

If blood CO_2 rises above normal levels, i.e. hypercapnia, vasodilation develops. This causes hyperaemia, a raised intracranial pressure, reduced cranial blood flow, and thus an increased demand for cerebral oxygen. The studies of Helmerhorst et al (9) and Schneider et al (10) found no significant difference in mortality between hypercapnia and normocapnia (OR 1.10, 95% CI 0.95-1.27 and OR 1.06, 95% CI 0.97-1.15, respectively). There was even a significantly higher percentage of survivors of hypercapnia discharged home than those of normocapnia (OR 1.16, 95% CI 1.03-1.32). Conversely, Roberts et al (11) did find a significant association between hypercapnia and a poor neurological

outcome (OR 2.20, 95% CI 1.03-4.71). In short, it appears that hypocapnia is associated with higher hospital mortality, while the relationship between hypercapnia and hospital mortality following cardiac arrest is not yet completely clear.

Oxygen (O_2):
As well as CO_2, O_2 plays an essential role in post-cardiopulmonary resuscitation injury. Two multicentre database studies show a significantly higher mortality if post-cardiopulmonary resuscitation hyperoxia is present. Bellomo et al (12) found a higher risk of mortality with an OR 1.5 (95%CI 1.3-1.8), and Kilgannon et al (13) an OR of 1.8 (95% CI 1.5-2.2). However, neither of these studies corrected for cardiac factors. Conversely, Roberts et al (14) did correct for these factors in their study, and found higher mortality to be associated with hyperoxia (relative risk [RR] 1.25, 95% CI 1.01-1.54), and also with a poorer neurological outcome (RR 1.24, 95% CI 1.13-1.35).

After a period of hypoxia the availability of oxygen can cause an increase in oxygen free radicals resulting in neural cell dysfunction and cell death. The risk of this type of damage is largest if hyperoxia is present. Bellomo et al (12) found a higher risk of mortality with an OR 1.5 (95%CI 1.3-1.8), and Kilgannon et al (13) an OR of 1.8 (95% CI 1.5-2.2). However, neither of these studies corrected for cardiac factors. Conversely, Roberts et al (14) did correct for these factors in their study and found higher mortality to be associated with hyperoxia (relative risk [RR] 1.25, 95% CI 1.01-1.54) and also with a poorer neurological outcome (RR 1.24, 95% CI 1.13-1.35).

Cerebral autoregulation:
Autoregulation reduces the harmful effects of hypoperfusion and hyperperfusion. During a circulatory arrest, cerebral autoregulation may disappear or shift to the right (higher mean arterial pressure [MAP] targets). If autoregulation cannot adapt itself sufficiently to the changes in blood pressure, the cerebral blood flow is no longer dependent on the cerebral pressure. The cerebral blood flow becomes dependent on passive pressure. This allows cerebral ischaemia and hyperaemia to develop. A recent study by Ameloot et al (15) found no significant difference in post-anoxic brain injury and neurological score at ICU discharge between the application of a MAP of 65mmHg versus 80-100mmHg, after OHCA.

Microcirculation and reperfusion:
Following cardiopulmonary resuscitation the function of the cerebrovascular endothelium is impaired. This causes the formation of microthrombi, cerebral vasoconstriction develops, and the blood-brain barrier function is reduced. This results in increased cerebrovascular vascular resistance, reduced cerebral blood flow, reduced cerebral oxygen supply, and vasogenic cerebral oedema, ultimately leading to ischaemia and cell death. (8)

Cerebral oedema:
Vasogenic cerebral oedema and cytotoxic cerebral oedema lead to a rise in intracranial pressure, lowering of cerebral perfusion pressure, reduction in cerebral blood flow, herniation, and may ultimately lead to brain death. (8) Experimental animal studies have shown that the administration of hypertonic saline may have a positive effect on the development of cerebral oedema following a circulatory arrest. (16) However, this was not confirmed by a prospective randomised study in humans. (17)

Another potentially preventative treatment option is the administration of glucocorticoids. In a retrospective propensity-matched study by Tsai et al (18), a significantly higher hospital survival was seen in patients treated with steroids (OR 1.71, 95% CI 1.42-2.05). A randomised controlled trial (RCT) by Mentzelopoulos et al (19) observed a higher likelihood of survival with a favourable neurological outcome in patients treated with vasopressin and methylprednisolone than in patients treated with placebo (OR 3.28, 95% CI 1.17-9.2). Whilst the effectiveness of administration of hypertonic saline during a circulatory arrest has not yet been sufficiently proven, the administration of steroids appears to have a positive effect on outcome.

Ischaemic time is tissue deterioration

A number of studies have shown that starting cardiopulmonary resuscitation as soon as possible results a higher number of favourable outcomes. The earlier resuscitation is started, the greater the chance of ROSC, and the shorter the time the patient needs to be resuscitated, the greater the chance of survival and neurologically favourable survival. (20, 21) A short no-flow time (time to resuscitation) and a short low-flow time (duration of cardiopulmonary resuscitation) are important to keep the impact of ischaemic injury as low as possible. After recognition of the cardiac arrest and start of cardiopulmonary resuscitation, an AED must be attached as quickly as possible. In this respect, it is of great importance that cardiopulmonary resuscitation is started by bystanders. In the Netherlands, the percentage of cardiopulmonary resuscitation procedures started by bystanders is very high; in 2012 this was >80% (5). If there is an initial shockable cardiac rhythm, a first defibrillation attempt within 3-5 minutes increases the chance of survival. (20) The duration of cardiopulmonary resuscitation is very important in obtaining a favourable outcome. The median duration of cardiopulmonary resuscitation in both OHCA and IHCA patients with favourable neurological survival is 6-13 minutes, this in comparison with a median duration of 15-31 minutes which is associated with unfavourable neurological survival. (21, 22)

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION

Indications for extracorporeal cardiopulmonary resuscitation

If there is no ROSC after 21 minutes of cardiopulmonary resuscitation, the possibility of implementing extracorporeal cardiopulmonary resuscitation (ECPR) may be considered. (23) ECPR is a technique whereby veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is initiated during cardiopulmonary resuscitation to support the function of heart and lungs, and thus covering both circulation and oxygenation. As this an invasive treatment with a high risk of complications and a high risk of mortality, the selection criteria are very strict. Although the international literature reports a wide variation in criteria, they often have factors in common. Table 1 shows the criteria used at the ErasmusMC:

Table 1 | Inclusion and exclusion criteria for ECPR

Inclusion:	Exclusion:
≤ 70 years old	Suspicion of, stage of, and/or treatment for malignancy
Last seen (i.e. no-flow time) < 5 min and/or signs of life (gasping, movement)	Critical vascular disease (ulcers on extremities and/or femoral artery not visible on ultrasound)
Start placing ECMO after a cardiopulmonary resuscitation duration of at least 20 minutes	End-tidal CO_2 <10 mmHg (1.3kPa) after 20 minutes resuscitation
Independent ADL prior to admission	Arrest caused by haemorrhagic shock
	Liver disease with MELD>30 or with Terlipressin
	Intracranial operation or CVA (ischaemic/haemorrhagic) <6 weeks
	Mediastinitis with sternum removal
	Cardiac arrest with 20 minutes of asystole
	Expected time from cardiopulmonary resuscitation to cannulation >60 min
	Technically impossible to cannulate

Extracorporeal membrane oxygenation (ECMO), activities of daily living (ADL), model for end-stage liver disease (MELD), cerebrovascular accident (CVA)

Technique and mechanism of action

When the ECPR procedure starts during cardiopulmonary resuscitation, the femoral vein and artery are usually accessed percutaneously under ultrasound guidance. Each of the vessels is cannulated (venous 21-25Fr and arterial 15-21Fr), and venous blood is drawn from the inferior vena cava. This blood is oxygenated and decarboxylated in the ECMO circuit and returned to the aorta through the arterial cannula. This retrograde flow reaches the aortic valve and therefore all the central organs (in particular the brain, heart, kidneys, and liver) are supplied with oxygen. In the meantime, the cause of the circulatory arrest can be looked for and treated (where possible).

Figure 2 shows a diagram of the VA-ECMO circuit in ECPR. The average level of blood flow (i.e. the number of litres of blood that is pumped around the body) of the ECMO after initiation of ECPR is set at 3-4L, with a sweep flow (the number of litres flowing through the oxygenator as a counterflow and thus the amount of CO_2 extracted) of 2L. Depending on the arterial blood gas values and the haemodynamic status of the patient, these values can be adjusted.

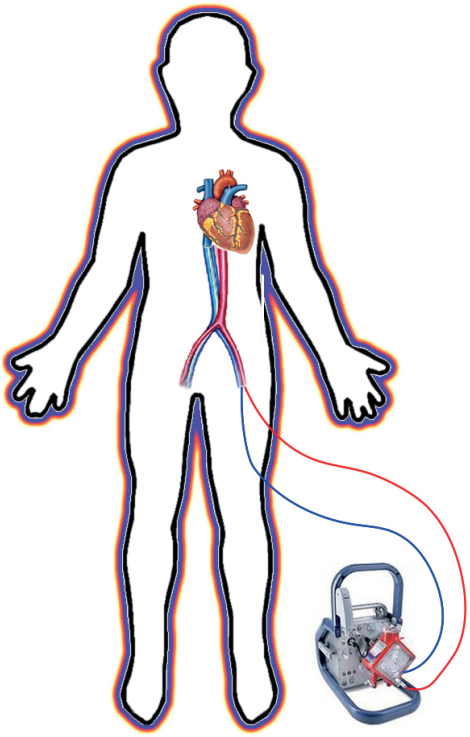


Figure 2 | Veno-arterial femoro-femoral ECMO

Often after ECMO has been initiated, the heart starts beating spontaneously due to the resumption of oxygen supply, and then pulsatility is visible on the arterial curve. If heart action is not directly seen after ECMO is initiated, the measured arterial blood pressure will consist of an equal systolic and diastolic pressure. This is because ECMO generates a constant flow, whereby pulsatility is absent. At the ErasmusMC, we aim to achieve a MAP of at least 60 mmHg using ECMO flow and in case they are needed also vasopressors. This is in order to generate the best possible pressure in the central organs.

When the arterial cannula is inserted, the femoral artery is often completely, or almost completely, occluded. In order to ensure that the leg distal of the arterial cannula is oxygenated, an antegrade cannula (6-8Fr.) is routinely placed percutaneously as soon as possible after ECMO has been initiated. This antegrade cannula is then attached to the arterial cannula of the ECMO system.

Evidence

Currently, only one RCT comparing ECPR to conventional cardiopulmonary resuscitation (CCPR) has been completed. (24) However, five international RCTs are now including patients, these include the INCEPTION trial (25) and the Prague OHCA study. (26) Besides the data from the first RCT, the data that are currently available originate from observational studies and meta-analyses. We will deal with the results of the studies on OHCA and IHCA separately.

OHCA

First, the studies in which OHCA patients were included. In the first RCT from Yannopoulos et al (24), a statistically significant higher survival was seen in ECPR than in CCPR treated patients (Hazard ratio 0.16, 95% confidence interval 0.06-0.41). The survivors who had undergone ECPR all had favourable neurological outcomes (CPC 1-2) at 6-month follow-up. Due to this large difference, this study with a sample size of 30 patients was ended prematurely. In the study by Sakamoto et al (27), a statistically significant higher survival rate was seen in patients treated with ECPR than in patients treated with CCPR (13.7% and 1.9%, p <0.01, respectively). The study of Kim et al (23), in which a propensity-matched analysis was performed, also showed higher neurologically favourable survival in ECPR patients than in CCPR patients (15.4% and 1.9%, p=0.01, respectively). However, a recent propensity-matched study conducted by Choi et al (28) found no significant difference in neurologically favourable survival (9% in ECPR patients and 2% in CCPR patients). However, they only included patients who did not regain ROSC before hospital arrival. The data on OHCA patients are still ambiguous.

IHCA

Second, the studies in which IHCA patients were included. One of the larger studies, that of Chen et al (29), shows higher neurologically favourable survival at hospital discharge in ECPR patients (23.7%) than in CCPR patients (10.6%, OR 2.6, 95% CI 1.1-6.7). The study by Shin et al (30) also shows a positive outcome for 28-day survival in ECPR patients (31.6%) in comparison with CCPR patients (10.0%, hazard ratio [HR]0.51 95%CI 0.33-0.78). They also report a statistically significant higher favourable neurological 1-year survival in ECPR patients (21.6%) than in CCPR patients (5.0%, HR 0.52 95%CI 0.35-0.78). A more recent study conducted by Blumenstein et al (31), in which a propensity-matched analysis was performed, found a higher favourable neurological survival in ECPR patients (21.2%) than in CCPR patients (13.5%). However, this difference was not statistically significant. This does not comprise definitive proof of the use of ECPR in comparison with CCPR in IHCA patients.

Reviews and guidelines

Just as in the above-mentioned individual studies, two recent reviews by Holmberg et al (32) and Chen et al (33) present varying data on the use of ECPR in OHCA and IHCA patients. This could be due to the size of the samples and their heterogeneity. In the 2015 and 2020 guidelines for resuscitation, the higher survival percentages - in particular the higher neurologically favourable survival - led the European Resuscitation Council (ERC) to consider ECPR as a potential therapy: "Extracorporeal CPR (ECPR) should be considered as a rescue therapy for those patients in whom initial ALS measures are unsuccessful and, or to facilitate specific interventions (e.g. coronary angiography and

percutaneous coronary intervention (PCI) or pulmonary thrombectomy for massive pulmonary embolism)." (34) However, the ERC also recognises that the quality of the current body of evidence is low.

Duration of resuscitation: an influential factor

One of the most important predictors of survival following cardiopulmonary resuscitation treated with ECPR, is the duration of cardiopulmonary resuscitation. (35) This covers the total duration of cardiac arrest, i.e. from calling the emergency services to the start of ECMO blood flow. A duration of cardiopulmonary resuscitation up to approximately 40 minutes seems to be a predictor of survival. (36) However, due to transportation times in particular in OHCA patients, in practice cardiopulmonary resuscitation often lasts >70 minutes. (36) A great deal of research is being done to find ways of shortening this time. This could be done by means of a resuscitation algorithm in a selected group of patients, but also by the prehospital initiation of ECMO. (35)

In a previous study which aimed at starting a resuscitation algorithm focused on as short a resuscitation time as possible in OHCA patients, neurologically favourable survival was seen in 42.0% in comparison with 15.3% in the group studied before the start of this algorithm. (38) Duration of cardiopulmonary resuscitation is also important in IHCA patients. In this group, bedside cannulation can be important in avoiding transport time prolonging time to ECPR initiation. (35) A propensity-matched study aiming at prehospital initiation of ECPR conducted by Lamhaut et al (39) reports no difference in survival between OHCA patients who are cannulated in hospital and those who are cannulated in the prehospital setting. This study found a significantly shorter duration of cardiopulmonary resuscitation for prehospital cannulation (70 minutes) than for cannulation in hospital (100 minutes). In addition, a significantly higher survival was seen following the introduction of a more aggressive ECPR strategy (38.0% versus 3.0% in the control period) (39). More research into the prehospital ECPR procedure is necessary.

In short, the level of evidence for ECPR which still only includes one small RCT and some other relatively small heterogeneous observational studies, is moderate. However, despite this there appears to be a solid trend towards a higher neurologically favourable survival in ECPR treatment than in CCPR treatment. Each individual patient with a refractory circulatory arrest will have to be critically assessed for eligibility for this ECPR therapy.

Complications of ECPR

This invasive treatment can be associated with a few major complications.

ECMO cannulation during resuscitation

First, performing an ECMO cannulation procedure during cardiopulmonary resuscitation is difficult, as due to cardiac compressions the patient is continually moving. This can cause difficulty in achieving ultrasound-guided access of the femoral artery and vein in this cardiopulmonary resuscitation setting. Also advancing the cannulas can be more problematic than during an 'elective' placement. The studies included in the review by Beyea et al (40) report unsuccessful cannulation in 3.0-55.6% of patients, in 19.1% ECMO flow could not be started, and problems with the circuit were present in 0.0-29.0%.

Arterial occlusion / limb complications

The introduction of an arterial cannula into the femoral artery can result in occlusion of the femoral artery distal from the cannula. This can lead to limb ischaemia and eventually to the development of compartment syndrome, even after a short occlusion time. Limb ischaemia has been described in 3.5-35.3%. (40, 41) In order to prevent this, in most cases it is necessary to place an antegrade cannula beneath the ECMO cannula, so the leg can be perfused.

Bleeding and coagulation complications

A third important group of complications involves bleeding and coagulation. During ECMO heparin has to be administered to prevent coagulation in the ECMO circuit. The damage which is caused during cardiopulmonary resuscitation (i.e. mechanical injury from the cardiopulmonary resuscitation procedure and pathophysiological injury due to ischaemia and reperfusion injury), and the use of coagulation products due to the critical illness and due to the use of ECMO may all result in life-threatening bleeding. Bleeding that required intervention was reported in 3.5-89.5% and thrombocytopenia was present in 20.8-76.3%. (40, 41) However, the initiation of ECMO can also cause coagulation complications. This is due to the higher risk of developing an embolism caused by contact with foreign material, and due to the higher risk of diffuse intravasal coagulation which occurs in 20.8-66.0% of patients. (40)

Other complications

Lastly, there are two further complications that occur regularly, but which are not necessarily related to ECPR. These are complications that occur in both ECPR and CCPR. Multi-organ dysfunction induced by ischaemia and reperfusion occurs in 26.9-42.1% of ECPR patients. (40) The other commonly-occurring cardiopulmonary resuscitation-related group of complications are the neurological complications. In 61.0% of ECPR patients, treatment is discontinued because there is no neurological recovery; 23.5% of ECPR patients suffer brain death, and a cerebrovascular accident occurs in 0.0-15.4% of these patients. (40)

OUTLINE OF THIS THESIS

This thesis starts with a national overview of cardiac arrest patients who need to be admitted to the ICU. These patients may be the more vulnerable cardiac arrest patients, as they require intensive care, but they might also represent those in whom in-hospital treatment could impact the outcome most. **Chapter 2** describes the number of patients who are admitted to ICU in the Netherlands following a cardiac arrest, and examines the 1-year survival and how it has changed over the years. These data are provided separately for OHCA and IHCA and give an indication of the relevance of the problem. In addition, **Chapter 3** draws a comparison between women and men with regard to incidence and outcome of this patient group.

A broader look at all resuscitations shows that duration of resuscitation is an extremely important factor in the determination of survival and neurological favourable survival. ECPR can be used if cardiopulmonary resuscitation lasts longer than 20 minutes. The results of studies so far, tend towards higher survival rates in ECPR treated patients than in CCPR treated patients. **Chapter 4** comprises a systematic review comparing the duration of cardiopulmonary resuscitation in ECPR and CCPR to give an indication when ECPR may be an additional therapy to CCPR.

Despite the fact many studies have been focusing on the added value of ECPR compared to CCPR, it remains unclear what the exact treatment strategy of ECPR should be in order to achieve the best possible results with this therapy. **Chapters 5-7** focus on the gas exchange during ECPR treatment as the first step towards the optimisation of ECPR settings. **Chapter 5** shows the course of oxygen availability in the mitochondria (the end station of oxygen, where it is converted to energy) of the skin, in an experimental setting in pigs treated with ECPR**.** In addition, we investigated the course of cerebral oxygenation during the first hours of ECPR in an international multicentre observational study, described in **Chapter 6**. Using ECPR, not only can oxygen be closely regulated, but carbon dioxide can also be closely regulated. **Chapter 7** shows the relationship of carbon dioxide with recovery of consciousness during the first six hours after initiation of ECPR.

The additional value of ECPR where cardiac arrest has a cardiac cause is currently being widely studied. However, ECPR can also be an important treatment option in other causes of cardiac arrest, e.g. if cardiac arrest is due to a massive pulmonary embolism. In these cases, ECPR recovers the circulation and bypasses the pulmonary embolism by which time can be bought until the pulmonary embolism is dissolved or removed. **Chapter 8** shows the effect of ECPR in relation to CCPR in patients suffering from cardiac arrest due to a pulmonary embolism. We examined differences in neurologically favourable survival between these two treatments. A systematic review and meta-analysis

aiming at the effect of ECMO in massive pulmonary embolism which is presented in **Chapter 9** shows that the effect on the survival is still not clear.

REFERENCES

1. Hartstichting. Jaarverslag 2018.
2. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Regional variation in the incidence and outcomes of in-hospital cardiac arrest in the United States. Circulation. 2015;131(16):1415-25.
3. Skogvoll E, Isern E, Sangolt GK, Gisvold SE. In-hospital cardiopulmonary resuscitation. 5 years' incidence and survival according to the Utstein template. Acta Anaesthesiol Scand. 1999;43(2):177-84.
4. Mandigers L, Termorshuizen F, de Keizer NF, Gommers D, dos Reis Miranda D, Rietdijk WJR, den Uil CA. A nationwide overview of 1-year mortality in cardiac arrest patients admitted to intensive care units in the Netherlands between 2010 and 2016. In press. 2019.
5. Blom MT, Beesems SG, Homma PC, Zijlstra JA, Hulleman M, van Hoeijen DA, et al. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. Circulation. 2014;130(21):1868-75.
6. Grasner JT, Lefering R, Koster RW, Masterson S, Bottiger BW, Herlitz J, et al. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation. 2016;105:188-95.
7. Zhu A, Zhang J. Meta-analysis of outcomes of the 2005 and 2010 cardiopulmonary resuscitation guidelines for adults with in-hospital cardiac arrest. Am J Emerg Med. 2016;34(6):1133-9.
8. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care. 2017;21(1):90.
9. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, Abu-Hanna A, de Keizer NF, de Jonge E. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. Crit Care. 2015;19:348.
10. Schneider AG, Eastwood GM, Bellomo R, Bailey M, Lipcsey M, Pilcher D, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. Resuscitation. 2013;84(7):927-34.
11. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Trzeciak S. Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. Circulation. 2013;127(21):2107-13.
12. Bellomo R, Bailey M, Eastwood GM, Nichol A, Pilcher D, Hart GK, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Crit Care. 2011;15(2):R90.
13. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA. 2010;303(21):2165-71.
14. Roberts BW, Kilgannon JH, Hunter BR, Puskarich MA, Pierce L, Donnino M, et al. Association Between Early Hyperoxia Exposure After Resuscitation From Cardiac Arrest and Neurological Disability: Prospective Multicenter Protocol-Directed Cohort Study. Circulation. 2018;137(20):2114-24.
15. Ameloot K, De Deyne C, Eertmans W, Ferdinande B, Dupont M, Palmers PJ, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. Eur Heart J. 2019;40(22):1804-14.
16. Nakayama S, Migliati E, Amiry-Moghaddam M, Ottersen OP, Bhardwaj A. Osmotherapy With Hypertonic Saline Attenuates Global Cerebral Edema Following Experimental Cardiac Arrest via Perivascular Pool of Aquaporin-4. Crit Care Med. 2016;44(8):e702-10.

17. Heradstveit BE, Guttormsen AB, Langorgen J, Hammersborg SM, Wentzel-Larsen T, Fanebust R, et al. Capillary leakage in post-cardiac arrest survivors during therapeutic hypothermia - a prospective, randomised study. Scand J Trauma Resusc Emerg Med. 2010;18:29.
18. Tsai MS, Chuang PY, Yu PH, Huang CH, Tang CH, Chang WT, et al. Glucocorticoid use during cardiopulmonary resuscitation may be beneficial for cardiac arrest. Int J Cardiol. 2016;222:629-35.
19. Mentzelopoulos SD, Malachias S, Chamos C, Konstantopoulos D, Ntaidou T, Papastylianou A, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA. 2013;310(3):270-9.
20. Perkins GD, Handley AJ, Koster RW, Castren M, Smyth MA, Olasveengen T, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 2. Adult basic life support and automated external defibrillation. Resuscitation. 2015;95:81-99.
21. Welbourn C, Efstathiou N. How does the length of cardiopulmonary resuscitation affect brain damage in patients surviving cardiac arrest? A systematic review. Scand J Trauma Resusc Emerg Med. 2018;26(1):77.
22. Adnet F, Triba MN, Borron SW, Lapostolle F, Hubert H, Gueugniaud PY, et al. Cardiopulmonary resuscitation duration and survival in out-of-hospital cardiac arrest patients. Resuscitation. 2017;111:74-81.
23. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. Crit Care. 2014;18(5):535.
24. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray T A, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. Lancet. 2020; 396(10265):1807-1816.
25. Bol ME, Suverein MM, Lorusso R, Delnoij TSR, Brandon Bravo Bruinsma GJ, Otterspoor L, et al. Early initiation of extracorporeal life support in refractory out-of-hospital cardiac arrest: Design and rationale of the INCEPTION trial. Am Heart J. 2019;210:58-68.
26. Belohlavek J, Kucera K, Jarkovsky J, Franek O, Pokorna M, Danda J, et al. Hyperinvasive approach to out-of hospital cardiac arrest using mechanical chest compression device, prehospital intraarrest cooling, extracorporeal life support and early invasive assessment compared to standard of care. A randomized parallel groups comparative study proposal. "Prague OHCA study". J Transl Med. 2012;10:163.
27. Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. Resuscitation. 2014;85(6):762-8.
28. Choi DS, Kim T, Ro YS, Ahn KO, Lee EJ, Hwang SS, et al. Extracorporeal life support and survival after out-of-hospital cardiac arrest in a nationwide registry: A propensity score-matched analysis. Resuscitation. 2016;99:26-32.
29. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet. 2008;372(9638):554-61.
30. Shin TG, Jo IJ, Sim MS, Song YB, Yang JH, Hahn JY, et al. Two-year survival and neurological outcome of in-hospital cardiac arrest patients rescued by extracorporeal cardiopulmonary resuscitation. Int J Cardiol. 2013;168(4):3424-30.

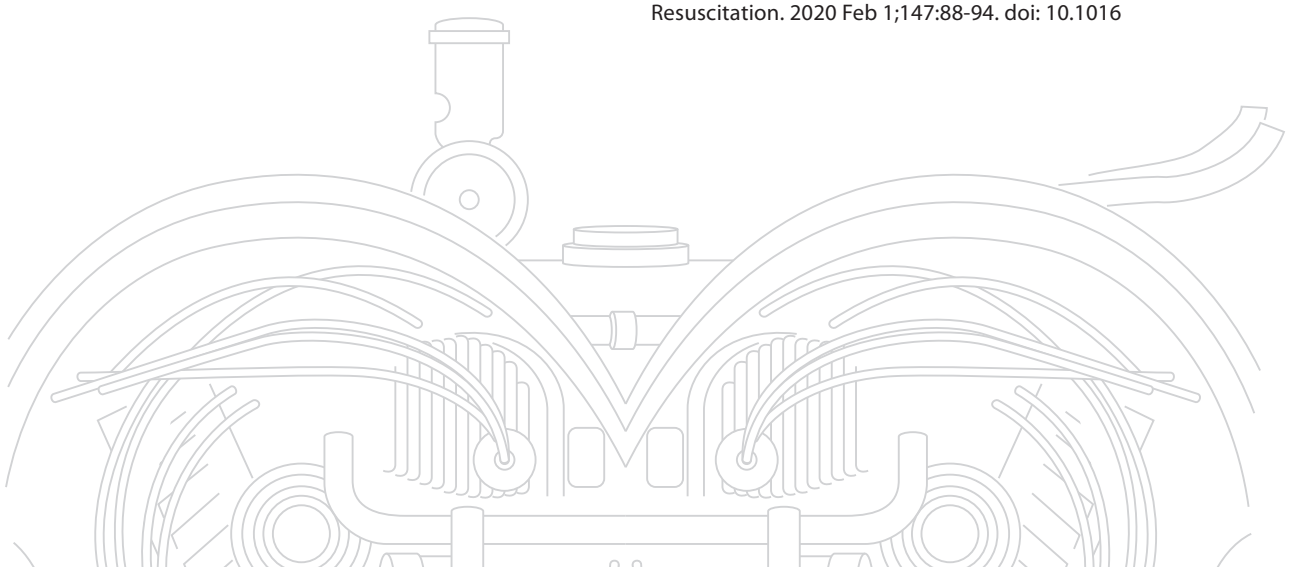
31. Blumenstein J, Leick J, Liebetrau C, Kempfert J, Gaede L, Gross S, et al. Extracorporeal life support in cardiovascular patients with observed refractory in-hospital cardiac arrest is associated with favourable short and long-term outcomes: A propensity-matched analysis. Eur Heart J Acute Cardiovasc Care. 2016;5(7):13-22.
32. Holmberg MJ, Geri G, Wiberg S, Guerguerian AM, Donnino MW, Nolan JP, et al. Extracorporeal cardiopulmonary resuscitation for cardiac arrest: A systematic review. Resuscitation. 2018;131:91-100.
33. Chen Z, Liu C, Huang J, Zeng P, Lin J, Zhu R, et al. Clinical Efficacy of Extracorporeal Cardiopulmonary Resuscitation for Adults with Cardiac Arrest: Meta-Analysis with Trial Sequential Analysis. Biomed Res Int. 2019;2019:6414673.
34. Soar J, Nolan JP, Bottiger BW, Perkins GD, Lott C, Carli P, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. Resuscitation. 2015;95:100-47.
35. Michels G, Wengenmayer T, Hagl C, Dohmen C, Bottiger BW, Bauersachs J, et al. Recommendations for extracorporeal cardiopulmonary resuscitation (eCPR): consensus statement of DGIIN, DGK, DGTHG, DGfK, DGNI, DGAI, DIVI and GRC. Clin Res Cardiol. 2019;108(5):455-64.
36. Kuroki N, Abe D, Iwama T, Suzuki K, Sugiyama K, Akashi A, et al. Association between delay to coronary reperfusion and outcome in patients with acute coronary syndrome undergoing extracorporeal cardiopulmonary resuscitation. Resuscitation. 2017;114:1-6.
37. Spangenberg T, Meincke F, Brooks S, Frerker C, Kreidel F, Thielsen T, et al. "Shock and Go?" extracorporeal cardio-pulmonary resuscitation in the golden-hour of ROSC. Catheter Cardiovasc Interv. 2016;88(5):691-6.
38. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascone RJ, Trembley A, et al. Coronary Artery Disease in Patients With Out-of-Hospital Refractory Ventricular Fibrillation Cardiac Arrest. J Am Coll Cardiol. 2017;70(9):1109-17.
39. Lamhaut L, Hutin A, Puymirat E, Jouan J, Raphalen JH, Jouffroy R, et al. A Pre-Hospital Extracorporeal Cardio Pulmonary Resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: An observational study and propensity analysis. Resuscitation. 2017;117:109-17.
40. Beyea MM, Tillmann BW, Iansavichene AE, Randhawa VK, Van Aarsen K, Nagpal AD. Neurologic outcomes after extracorporeal membrane oxygenation assisted CPR for resuscitation of out-of-hospital cardiac arrest patients: A systematic review. Resuscitation. 2018;130:146-58.
41. Ellouze O, Vuillet M, Perrot J, Grosjean S, Missaoui A, Aho S, et al. Comparable Outcome of Out-of-Hospital Cardiac Arrest and In-Hospital Cardiac Arrest Treated With Extracorporeal Life Support. Artif Organs. 2018;42(1):15-21.

Chapter 2

A nationwide overview of 1-year mortality in cardiac arrest patients admitted to intensive care units in the Netherlands between 2010 and 2016

Loes Mandigers, Fabian Termorshuizen, Nicolette F. de Keizer, Diederik Gommers, Dinis dos Reis Miranda, Wim J.R. Rietdijk, Corstiaan A. den Uil

Resuscitation. 2020 Feb 1;147:88-94. doi: 10.1016



ABSTRACT

Aim Worldwide, cardiac arrest (CA) remains a major cause of death. Most post-CA patients are admitted to the intensive care unit (ICU). The aim of this study is to describe mortality rates and possible changes in mortality rates in patients with CA admitted to the ICU in the Netherlands between 2010 and 2016.

Methods In this study, we included all adult CA patients registered in the National Intensive Care Evaluation (NICE) registry who were admitted to ICUs in the Netherlands between 2010 and 2016. The primary outcome was 1-year mortality which was analysed by Cox regression. The secondary outcomes were ICU mortality and hospital mortality. Hospital mortality was analysed by binary logistic regression analysis. Patients were stratified by whether they experienced in-hospital cardiac arrest (IHCA) or out-of-hospital cardiac arrest (OHCA). Finally, the outcome over calendar time was assessed for both groups.

Results We included 26,056 CA patients: 10,618 (40.8%) IHCA patients and 14,482 (55.6%) OHCA patients. The 1-year mortality rate was 57.5%: 59.0% for IHCA and 56.4% for OHCA, $p<0.01$. This mortality rate remained stable between 2010 and 2016 for IHCA ($p=0.31$) and declined for OHCA patients ($p=0.01$). The hospital mortality rate was 50.3%: 50.5% for IHCA and 50.2% for OHCA, $p=0.66$. This mortality rate remained stable between 2010-2016 for IHCA ($p=0.21$) and decreased for OHCA patients ($p<0.01$). An additional analysis with calendar year as a continuous variable showed a mortality decline of 1.56% per calendar year for 1-year mortality.

Conclusion This nationwide registry cohort study reported a 57.5% 1-year mortality rate for CA patients admitted to the ICU between 2010 and 2016. We reported a decline in 1-year mortality for OHCA patients in these years.

Keywords: Cardiac Arrest, Heart Arrest, Intensive Care Units, ICU, Mortality, 1-year mortality

INTRODUCTION

Sudden cardiac arrest (CA) remains a major cause of death worldwide (World Health Organization, WHO). In Europe, approximately 375,000 adults suffer annually from CA [1, 2]. Mortality rates in patients admitted to the hospital due to CA have been reported to be between 58-61% [3-5]. If these CA patients are admitted to the intensive care unit (ICU), mortality rates vary between 53-66% [6-8]. Of all surviving CA patients 25-75% have poor neurological outcomes and a large portion suffers from long-term side effects [9-11], such as post-traumatic stress disorder (PTSD) [12, 13], impaired quality of life [14], and lower physical and mental functioning [15].

Recent studies have examined characteristics that are associated with the mortality of CA patients. More specifically, these studies focused on differences in patient characteristics [16, 17], the location of the CA (in- or out-of-hospital) [18-20], and hospital characteristics [4, 6]. Generally, these studies provide data on all CA patients, including patients who died before hospital admission. However, there is no recent study showing a nationwide overview of CA patients admitted to the ICU.

In the Netherlands, 4.6% of all patients admitted to the ICU have CA as primary diagnosis [21]. The outcomes of these patients are highly interesting because they survived the first episode of CA (namely, cardiopulmonary resuscitation). However, they are prone to haemodynamic deterioration/instability, ischaemia/reperfusion injury, and neurological damage. In addition, large-scale data on the outcomes in this patient group are lacking. This information would be particularly relevant given recent changes in guidelines and treatments, such as targeted temperature management (TTM) [22]. Therefore, we analysed a large national database to investigate the mortality rates in CA patients (both IHCA and OHCA) admitted to ICUs in the Netherlands.

METHODS

Patient data

In this study, we used patient data included in the National Intensive Care Evaluation (NICE) registry [21]. This is a national quality registry in the Netherlands for ICU care, in which demographics, physiological and diagnostic data, patient outcomes, and ICU characteristics are registered. The data are prospectively collected with a primary focus on monitoring the quality of care in the ICU. We retrospectively analysed the data from approximately 85% of ICU departments in 2010 to 100% of ICU departments in 2016 in the Netherlands [21, 23].

We included all adult CA patients (≥18 years) who were admitted to the participating ICUs from 2010 to 2016. This period was selected because starting in 2010, we were

able to determine 1-year mortality [21, 23]. The Scientific Board of the NICE Foundation (number 2018-01) and the Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands (number MEC-2018-1228) approved this study and the need for informed consent was waived.

Characteristics and clinical outcomes

We included patient characteristics (i.e., sex, age, body mass index (BMI), and history (e.g., renal insufficiency/dialysis, chronic obstructive pulmonary disease (COPD)/chronic respiratory insufficiency, cardiovascular insufficiency, liver cirrhosis, (haematologic) malignancy, and immunologic insufficiency)), admission characteristics (i.e., Acute Physiology and Chronic Health Evaluation (APACHE IV) score, estimated mortality rate and diagnoses within 24h of ICU admission (e.g., acute kidney injury (AKI), the use of mechanical ventilation, infection, the administration of thrombolytic therapy, vasoactive medication use, and academic/non-academic hospital), and clinical outcomes (length of stay, ICU mortality, hospital mortality, and 1-year mortality). Supplementary Material Table A shows the definitions of these variables.

First, we included all patients (henceforth referred to as CA patients) registered with an admission diagnosis of CA or cardiopulmonary resuscitation (CPR). Next, we stratified the characteristics and clinical outcomes for IHCA and OHCA patients. However, IHCA and OHCA were not encoded in the NICE registry. Therefore, we defined IHCA as an admission diagnosis of CA or CPR, with admission origin within the hospital, excluding the emergency department (ED). OHCA was defined as an admission diagnosis of CA or CPR, with an admission origin in the ED or home. Hospital and 1-year mortality rates were calculated, and hazard ratios (HRs) per year were assessed relative to the year 2010. We determined the 1-year mortality by using an administrative claims database that is linked to the NICE registry (i.e., Vektis data) [23, 24].

Statistical analysis

All characteristics and clinical outcomes were described as counts (%) and medians (interquartile range, IQR), as appropriate. The data are shown for the total sample and were stratified by IHCA and OHCA. Patients with unknown locations of CA were excluded from the stratified analyses. To test for differences between IHCA and OHCA patients, we used Chi-square and Wilcoxon tests for categorical and continuous variables, respectively.

The primary outcome was 1-year mortality. We examined the mortality trend over time using a Cox proportional hazard model with calendar years from 2010 to 2016 as an independent variable. For each calendar year, a dummy variable was included. The variables we included in each of the regression models are stated in the Supplementary Material Appendix 1. We built these regression models in two ways: (1) univariable analysis and (2) multivariable analysis adjusting for demographic and clinical characteristics

and including a random intercept for hospital. This was done to take the correlation between patients from the same hospital into account. To check whether the selection of different hospitals across the calendar years might have influenced the results, we performed a sensitivity analysis restricted to hospitals that registered their patients in each calendar year of the study period (2010-2016). We present the hazard ratios (HR) and 95% Confidence Intervals (95% CI) of model (2), as this was the best possible representation of all the available data. The adjusted effect of calendar year as a categorical variable on the hazard of death was tested by means of a post-estimation Wald test with number of degrees of freedom equal to the number of calendar years minus 1 (for the reference category=2010). In this test, calendar year was included as categorical variable without assuming a linear trend. As an additional analysis, we performed Cox proportional hazards regression, including calendar year as a continuous variable for the different outcomes. These analyses enabled us to estimate the average change in mortality rates per year over time. All models were analysed for IHCA and OHCA separately. IHCA and OHCA were not compared in these analyses because of the non-registered characteristics relevant to CA.

Our secondary outcomes were ICU mortality and hospital mortality. For ICU mortality, we only present a percentage to make a rough comparison with hospital mortality. For hospital mortality, we analysed the data using a binary logistic regression model and presented the Odd Ratios (ORs) and 95% CIs. All analyses were performed using R-studio. A p-value<0.05 was considered statistically significant.

RESULTS

Between 2010 and 2016, a total of 567,856 patients were included in the NICE registry, and 26,056 (4.6%) of those patients were admitted due to CA: 10,618 (40.8%) IHCA patients and 14,482 (55.6%) OHCA patients. Data from 956 (3.6%) patients were excluded from the comparison of OHCA versus IHCA due to an unknown location of the CA.

Descriptive statistics

Table 1 presents the patient characteristics of all CA patients and then those of the patients stratified into the IHCA and OHCA groups. The majority of the CA patients were male, with an average age of 67 years at the time of the arrest. IHCA patients were older and had overall more comorbidities than OHCA patients. Table 2 presents the admission characteristics. The median APACHE IV estimated mortality probability was 0.75. The majority of patients had a Glasgow coma scale (GCS) at admission of ≤ 5 (61.7%). At admission, 87.1% of the patients were mechanically ventilated. Table 3 presents the clinical outcomes. The median length of ICU stay was 64h (IQR 21-134) and the median hospital length of stay was 6 days (IQR 2-15).

Table 1 | Patient characteristics

	Total sample *	IHCA	OHCA	p-value
Patients 2010-2016	26,056	10,618	14,482	
Age (IQR)	67 (57-76)	69 (59-77)	66 (55-75)	<0.01
Gender, male (%)	17,320 (66.5)	6731 (63.4)	9967 (68.8)	<0.01
BMI (IQR)	25.7 (23.4-28.7)	25.7 (23.4-28.9)	25.7 (23.4-28.4)	0.99
BMI missing (%)		711 (6.6)	985 (6.8)	
History (N= 26,056)				
Cardiovascular insufficiency (%)	2291 (8.8)	1160 (10.9)	1030 (7.1)	<0.01
COPD /respiratory insufficiency (%)	4070 (15.6)	1894 (17.8)	2042 (14.1)	<0.01
Renal insufficiency (%)	1802 (6.9)	976 (9.2)	765 (5.3)	<0.01
Liver cirrhosis (%)	273 (1)	138 (1.3)	125 (0.9)	0.01
(Hematologic) malignancy (%)	1092 (4.2)	692 (6.5)	374 (2.6)	<0.01
Immunodeficiency (%)	1316 (5.1)	779 (7.3)	500 (3.5)	<0.01

* In 956 patients, it was unknown if the cardiac arrest occurred in- or outside the hospital; these patients were excluded from the analyses.

Primary outcome: 1-year mortality

Within one year after ICU admission, 14,974 (57.5%) CA patients died. This 1-year mortality was significantly higher in IHCA patients (59.0%) versus OHCA patients (56.4%, p<0.01). In Supplementary Material Fig. A, we present the Kaplan-Meier curve for 1-year mortality for IHCA and OHCA patients. Fig. 1 presents the analysis of model (2), as described in the methods section, of 1-year mortality for IHCA and OHCA patients separately. In IHCA patients no significant differences over time were observed. In OHCA patients a significant decrease in 1-year mortality between 2010 and 2016 was observed (all p<0.02). The sensitivity analyses restricting to hospitals that recruited patients the full study period gave similar results.

Secondary outcomes: ICU mortality, hospital mortality, and additional analyses

Of the total sample, 11,681 (44.8%) CA patients died in the ICU. The ICU mortality rates were slightly lower for IHCA than for OHCA patients (44.2% versus 45.4%, respectively, p=0.05). During their hospital admission, 13,072 (50.3%) CA patients died. This hospital mortality rate was comparable in IHCA and OHCA patients (50.5% versus 50.2%, respectively, p=0.66).

For hospital mortality, there was no significant trend in IHCA patients over time (Wald test (df) 8.39 (6), p=0.21). However, the analysis for hospital mortality in OHCA patients with calendar year as a categorised variable showed significant differences between the calendar years Wald test (df) 22.78 (6), p<0.01). Inspecting the Odds Ratios we found a decreasing trend, as shown in Fig. 2.

Table 2 | Admission characteristics in CA patients admitted to the ICU between 2010-2016

	Total sample*	IHCA	OHCA	p-value
APACHE IV estimated mortality rate (IQR)	0.75 (0.45-0.89)	0.71 (0.32-0.90)	0.77 (0.54-0.88)	<0.01
Admission type				<0.01
Medical	23,156 (88.9)	7968 (75.0)	14,291 (98.7)	
Urgent surgical	1,682 (6.5)	1,517 (14.3)	122 (0.8)	
Elective surgical	1,103 (4.2)	1,088 (10.2)	6 (<1)	
Diagnosis on admission				
GCS ≤ 5 (%)	16,066 (61.7)	5333 (50.2)	10,167 (70.2)	<0.01
GCS 6-14 (%)	4057 (15.6)	1736 (16.3)	2148 (14.8)	
GCS 15 (%)	5391 (20.7)	3327 (31.3)	1851 (12.8)	
GCS missing (%)		222 (2.1)	316 (2.2)	
Dysrhythmia (%)	13,343 (51.2)	5138 (48.4)	7676 (53)	<0.01
Mechanical ventilation (%)	22,701 (87.1)	8696 (81.9)	13,189 (91.1)	<0.01
CVA (%)	1053 (4.1)	455 (4.3)	558 (3.9)	0.10
Intracranial mass (%)	708 (2.7)	264 (2.5)	421 (2.9)	0.04
Gastro intestinal bleeding (%)	480 (1.8)	277 (2.6)	189 (1.3)	<0.01
Diabetes (%)	4438 (17)	2045 (19.3)	2221 (15.3)	<0.01
Diagnosis at 24h of ICU admission				
GCS ≤ 5 (%)	13,541 (52)	4615 (43.5)	8420 (58.1)	<0.01
GCS 6-14 (%)	4198 (16.1)	1621 (15.3)	2407 (16.6)	
GCS 15 (%)	7664 (29.4)	4095 (38.6)	3312 (22.9)	
AKI (%)	4617 (17.7)	2263 (21.3)	2188 (15.1)	<0.01
Mechanical ventilation (%)	23,666 (90.8)	9229 (86.9)	13,592 (93.9)	<0.01
Infection (%)	2768 (10.6)	1641 (15.5)	1062 (7.3)	<0.01
Vasoactive medication (%)	18,962 (72.8)	7640 (72)	10,652 (73.6)	<0.01
Thrombolytic therapy (%)	1354 (5.2)	560 (5.3)	756 (5.2)	0.87
Academic hospital (%)	7956 (23.9)	3102 (22.2)	4656 (26.1)	<0.01

* In 956 patients, it was unknown if the cardiac arrest occurred in- or outside the hospital; these patients were excluded from the analyses.

Next, the results of the additional analysis with calendar year as a continuous variable showed no significant trend in 1-year mortality over time for IHCA patients (HR 0.99, 95% CI 0.98-1.00, p=0.13). Furthermore, it confirmed the observed decline in 1-year mortality over time for OHCA patients (HR 0.98, 95% CI 0.97-1.00, p<0.01). This HR shows a reduction in 1-year mortality of 1.56% per year over the study period.

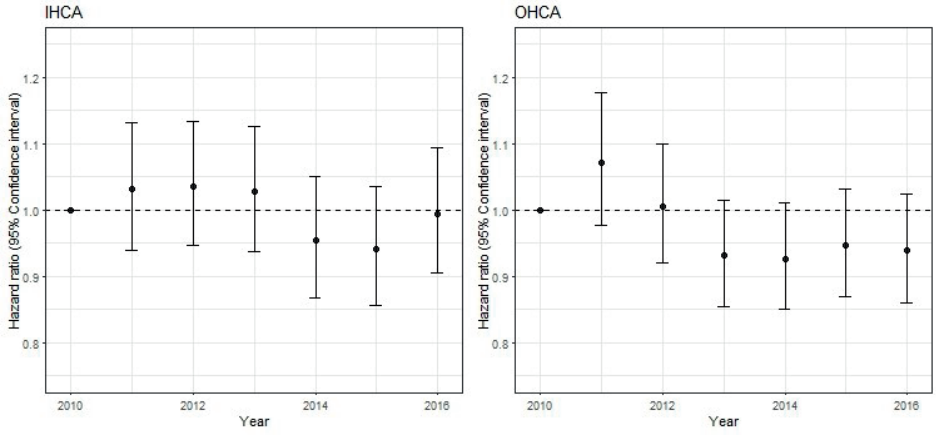


Figure 1 | Multivariable Cox regression analysis of 1-year mortality for IHCA (p=0.31) and OHCA (p=0.01) over calendar time

As we found a decreasing trend in 1-year mortality for OHCA patients, we decided to perform an additional Cox regression using left truncation at the time of hospital discharge (i.e., only selecting the hospital survivors), see Supplementary Material Fig. B. This shows that a significant trend over time remains present (p<0.01).

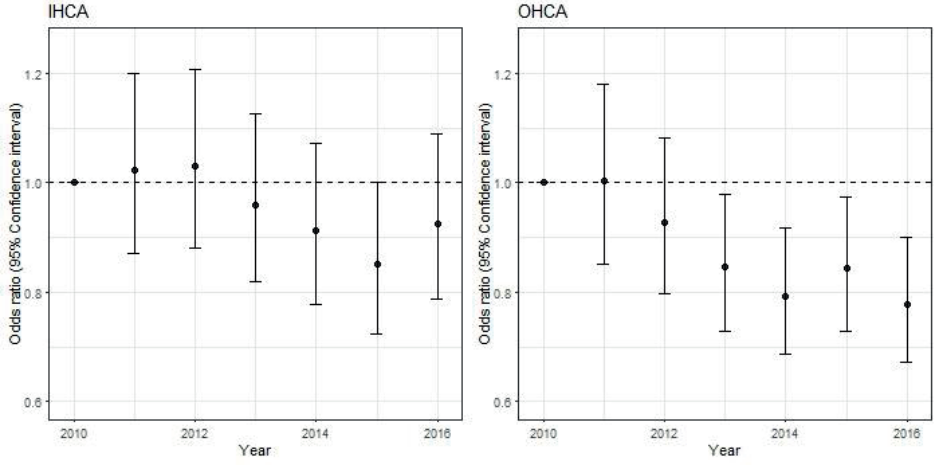


Figure 2 | Binary logistic regression analysis of hospital mortality for IHCA (p=0.21) and OHCA (p<0.01) over calendar time.

DISCUSSION

This is the first large nationwide study on 1-year mortality rates of CA patients admitted to the ICU, and it was performed in the Netherlands between 2010 and 2016. The secondary outcomes we described were ICU mortality and hospital mortality. Overall, we found reasonable mortality rates and a significant decrease in 1-year mortality of OHCA patients between 2010 and 2016.

As a primary outcome, we reported a 1-year mortality rate of 57.5% in the total cohort. This 1-year mortality rate was slightly higher in IHCA patients than in OHCA patients. Though in a smaller sample, Engsig et al [25] investigated long-term outcomes and showed comparable 1-year mortality rates, which were similar for IHCA and OHCA patients (47% and 51%, respectively). We found a stable 1-year mortality rate between 2010 and 2016 for IHCA patients. Remarkably, the 1-year mortality of OHCA patients decreased in this time period, and this decrease persisted after limiting the analysis to the hospital survivors (see Supplementary Material Fig. C). This could point to a healthier discharged CA patient population.

As a secondary outcome, we studied hospital mortality, which was approximately 50% in the total cohort, as well as for both IHCA and OHCA patients separately. In addition, we found that hospital mortality was stable for IHCA patients between 2010 and 2016. For OHCA, we found a decreasing trend in hospital mortality in this time period. These mortality rates are in line with those in previous studies reporting hospital mortality rates in CA patients [7, 26-28].

In this study, we found a median APACHE IV estimated mortality rate of 0.75, which is much higher than the observed hospital mortality rate. Zimmerman et al [29] validated this APACHE IV score for CA patients in the United States. However, Brinkman et al [30] showed poor APACHE IV score performance in CA patients in the Netherlands. Our study was performed with the same data registry as was the study by Brinkman et al [30]. Because the APACHE IV score is not validated for CA patients in the Netherlands, this difference in expected and observed mortality could be explained.

Given the limitations of a nationwide observational dataset, we could not fully study the underlying cause for the reduction in mortality among the OHCA patients. However, we would like to discuss possible explanations for the differences in mortality rates between IHCA and OHCA patients and the decline in 1-year and hospital mortality of OHCA patients.

First, although we have corrected our analyses for relevant patient characteristics, CA characteristics may have changed during the study period. For example, in the Netherlands public awareness of CA is increasing over time due to nationwide education [31]. This could have resulted in a higher percentage of bystander life support and automated external defibrillator (AED) use. In turn this may have resulted in a shorter

time to the return of spontaneous circulation (ROSC), which we were unable to examine in the present study.

Second, AED use may have contributed to the decrease in the mortality rate in OHCA patients. Despite the promising results, worldwide AED use is still quite limited compared to the Netherlands [18, 20, 32, 33]. Blom et al [32] showed that in the Netherlands, the use of AEDs and hospital survival both increased over time in the period 2006-2012. In this same period, Ringh et al [34] reported an increase in the number and use of public AEDs and its effect on mortality rates in Sweden. Taken together, in our opinion, the widespread use of AEDs in the Netherlands probably contributed to the decrease in 1-year mortality in OHCA patients found in our study.

Another possible explanation for the decrease in the mortality rate in OHCA patients is the predominant use of targeted temperature management (TTM), compared to its limited use in IHCA patients. Mounting research has been performed on temperature management in CA patients [8, 22, 27, 28, 35-37], mostly these studies have been performed in OHCA patients. As stated in the 2015 guidelines, since 2010, a temperature of 32-34 degrees Celsius is recommended, which changed in 2015 to 36 degrees Celsius [22]. Several studies showed different results in goal temperatures for the TTM, but they all recommend using hypothermia or normothermia and preventing hyperthermia [8, 22, 35-37]. However, Engsig et al [25] showed no difference in OHCA and IHCA patients. Wang et al [38] showed a benefit for TTM in IHCA patients, but TTM was performed in only 3.2% of the patients. Chan et al [39] also showed a low TTM rate in IHCA patients and they found no association between TTM and survival or neurological outcomes. In the Netherlands, it is difficult to pinpoint the exact date of the implementation of the TTM guidelines, as shown by Pickkers et al [8], while at the same time many hospitals started using TTM for OHCA patients during our study period. Thus, this may have contributed to the differences in mortality trends between 2010 and 2016 in IHCA and OHCA patients found in our study. Taken together, TTM is used more often in OHCA patients and has shown some promising results. However, TTM is not used as often in IHCA patients, although this may actually be a promising treatment strategy for these patients too.

Fourth, in the Netherlands, no studies have been conducted on the effect of cardiac rehabilitation on the mortality rate specifically in CA patients. However, some studies on the effect of cardiac rehabilitation on mortality in acute coronary syndrome and cardiac surgery patients showed a lower mortality rate for those who received cardiac rehabilitation compared to those who did not [40, 41]. OHCA patients are more likely to receive cardiac rehabilitation [10, 42]. For these patients, a cardiac cause such as coronary disease, was most likely the reason for the CA. Given the decrease in 1-year mortality rates in our study, which persisted after selecting only hospital survivors, it is likely that

rehabilitation therapy contributed to this lower 1-year mortality in OHCA patients. It may clarify the difference between IHCA and OHCA outcomes.

Finally, during the last decade the treatment of coronary diseases improved. Advances in coronary revascularization and adherence to secondary prevention guidelines (including internal cardiac defibrillatory therapy) may have contributed to an important improvement in mortality rates in OHCA patients, while this is not the case in IHCA patients.

Future research may study the possible effects of pre-ICU characteristics and in- and post-hospital treatments on short- and long-term mortality rates of CA patients admitted to the ICU. Our linear trend should be regarded as a crude average of various up- and downward movements of the graph. In the restricted time frame of our analysis, these movements are hard to interpret as coincidence or due to specific causes. For this reason, no nonlinear trends were included in the analysis. In case a study can be performed with more data relevant to CA from a longer time period a more specific trend analysis (e.g. non-linear trend) will be informative.

Limitations

As in every (retrospective) study, this research had several limitations. First, as mentioned before, the NICE registry is aimed at quality of care at the ICU and not all characteristics relevant to CA are registered. In particular, we did not have access to the following characteristics: witnessed/unwitnessed CA, CPR delay, time until ROSC, primary cardiac rhythm, cardiac interventions, AED use, mechanical compression device use and cause of arrest. These characteristics are important when studying the determinants of the outcome of CA. Therefore, in future research, these characteristics must be taken into account.

Second, the NICE registry does not record whether the CA took place in- or out-of-hospital. We had to determine this with the best possible approximation. With this method, we expect that some of the IHCA patients were misclassified as OHCA. Most of the patients admitted at the ICU with admission-origin ED were OHCA patients; however, some of them experienced CA while in the ED. We assume that this issue has limited consequences for the results, but we cannot exclude the possibility of some bias.

Third, in this study, we could only report mortality rates. Unfortunately, there were no data available on neurological outcomes; therefore, we were unable to report survival with good neurological outcome.

Finally, in some hospitals in the Netherlands, post-CA patients are admitted to the cardiac care unit instead of the ICU. We were unable to estimate how many patients were in this group as this is not recorded or these data were not available to the authors. As a consequence, this could result in different numbers of patients in comparison to the CA numbers reported in other studies.

CONCLUSION

This nationwide registry cohort study reported a 57.5% 1-year mortality rate for CA patients admitted to the ICU between 2010 and 2016. We reported a decline in 1-year mortality for OHCA patients in these years.

REFERENCES

1. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation. 2005;67:75-80.
2. Nolan JP, Soar J, Smith GB, Gwinnutt C, Parrott F, Power S, et al. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. Resuscitation. 2014;85:987-92.
3. Guterman EL, Kim AS, Josephson SA. Neurologic consultation and use of therapeutic hypothermia for cardiac arrest. Resuscitation. 2017;118:43-8.
4. Kurz MC, Donnelly JP, Wang HE. Variations in survival after cardiac arrest among academic medical center-affiliated hospitals. PLoS One. 2017;12:e0178793.
5. Rush B, Ashkanani M, Romano K, Hertz P. Utilization of electroencephalogram post cardiac arrest in the United States: A nationwide retrospective cohort analysis. Resuscitation. 2017;110:141-5.
6. Schober A, Holzer M, Hochrieser H, Posch M, Schmutz R, Metnitz P. Effect of intensive care after cardiac arrest on patient outcome: a database analysis. Crit Care. 2014;18:R84.
7. Straney LD, Bray JE, Finn J, Bernard S, Pilcher D. Trends in intensive care unit cardiac arrest admissions and mortality in Australia and New Zealand. Crit Care Resusc. 2014;16:104-11.
8. van der Wal G, Brinkman S, Bisschops LL, Hoedemaekers CW, van der Hoeven JG, de Lange DW, et al. Influence of mild therapeutic hypothermia after cardiac arrest on hospital mortality. Crit Care Med. 2011;39:84-8.
9. Perucki WH, Hiendlmayr B, O'Sullivan DM, Gunaseelan AC, Fayas F, Fernandez AB. Magnesium Levels and Neurologic Outcomes in Patients Undergoing Therapeutic Hypothermia After Cardiac Arrest. Ther Hypothermia Temp Manag. 2018;8:14-7.
10. Radeschi G, Mina A, Berta G, Fassiola A, Roasio A, Urso F, et al. Incidence and outcome of in-hospital cardiac arrest in Italy: a multicentre observational study in the Piedmont Region. Resuscitation. 2017;119:48-55.
11. Wang CH, Huang CH, Chang WT, Tsai MS, Yu PH, Wu YW, et al. Outcomes of adults with in-hospital cardiac arrest after implementation of the 2010 resuscitation guidelines. Int J Cardiol. 2017;249:214-9.
12. Gamper G, Willeit M, Sterz F, Herkner H, Zoufaly A, Hornik K, et al. Life after death: posttraumatic stress disorder in survivors of cardiac arrest--prevalence, associated factors, and the influence of sedation and analgesia. Crit Care Med. 2004;32:378-83.
13. Mongardon N, Dumas F, Ricome S, Grimaldi D, Hissem T, Pene F, et al. Postcardiac arrest syndrome: from immediate resuscitation to long-term outcome. Ann Intensive Care. 2011;1:45.
14. Wachelder EM, Moulaert VR, van Heugten C, Verbunt JA, Bekkers SC, Wade DT. Life after survival: long-term daily functioning and quality of life after an out-of-hospital cardiac arrest. Resuscitation. 2009;80:517-22.
15. Bunch TJ, White RD, Gersh BJ, Meverden RA, Hodge DO, Ballman KV, et al. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. N Engl J Med. 2003;348:2626-33.
16. Al-Dury N, Rawshani A, Israelsson J, Stromsoe A, Aune S, Agerstrom J, et al. Characteristics and outcome among 14,933 adult cases of in-hospital cardiac arrest: A nationwide study with the emphasis on gender and age. Am J Emerg Med. 2017;35:1839-44.
17. Libungan B, Lindqvist J, Stromsoe A, Nordberg P, Hollenberg J, Albertsson P, et al. Out-of-hospital cardiac arrest in the elderly: A large-scale population-based study. Resuscitation. 2015;94:28-32.
18. Hawkes C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. Resuscitation. 2017;110:133-40.

19. Kazaure HS, Roman SA, Sosa JA. Epidemiology and outcomes of in-hospital cardiopulmonary resuscitation in the United States, 2000-2009. Resuscitation. 2013;84:1255-60.
20. Ro YS, Shin SD, Song KJ, Lee EJ, Kim JY, Ahn KO, et al. A trend in epidemiology and outcomes of out-of-hospital cardiac arrest by urbanization level: a nationwide observational study from 2006 to 2010 in South Korea. Resuscitation. 2013;84:547-57.
21. NICE. Data in beeld. 2016.
22. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med. 2015;41:2039-56.
23. van de Klundert N, Holman R, Dongelmans DA, de Keizer NF. Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol. 2015;44:1850-h.
24. Karakus A, Haas LEM, Brinkman S, de Lange DW, de Keizer NF. Trends in short-term and 1-year mortality in very elderly intensive care patients in the Netherlands: a retrospective study from 2008 to 2014. Intensive Care Med. 2017;43:1476-84.
25. Engsig M, Soholm H, Folke F, Gadegaard PJ, Wiis JT, Molin R, et al. Similar long-term survival of consecutive in-hospital and out-of-hospital cardiac arrest patients treated with targeted temperature management. Clin Epidemiol. 2016;8:761-8.
26. Carr BG, Goyal M, Band RA, Gaieski DF, Abella BS, Merchant RM, et al. A national analysis of the relationship between hospital factors and post-cardiac arrest mortality. Intensive Care Med. 2009;35:505-11.
27. Jones D, Bhasale A, Bailey M, Pilcher D, Anstey MH. Effect of a National Standard for Deteriorating Patients on Intensive Care Admissions Due to Cardiac Arrest in Australia. Crit Care Med. 2018;46:586-93.
28. Salter R, Bailey M, Bellomo R, Eastwood G, Goodwin A, Nielsen N, et al. Changes in Temperature Management of Cardiac Arrest Patients Following Publication of the Target Temperature Management Trial. Crit Care Med. 2018;46:1722-30.
29. Zimmerman JE, Kramer AA, McNair DS, Malila FM, Shaffer VL. Intensive care unit length of stay: Benchmarking based on Acute Physiology and Chronic Health Evaluation (APACHE) IV. Crit Care Med. 2006;34:2517-29.
30. Brinkman S, Bakhshi-Raiez F, Abu-Hanna A, de Jonge E, Bosman RJ, Peelen L, et al. External validation of Acute Physiology and Chronic Health Evaluation IV in Dutch intensive care units and comparison with Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II. J Crit Care. 2011;26:105 e11-8.
31. Hartstichting. Forse toename snelle hulp bij een hartstilstand. Hartstichting; 2019.
32. Blom MT, Beesems SG, Homma PC, Zijlstra JA, Hulleman M, van Hoeijen DA, et al. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. Circulation. 2014;130:1868-75.
33. Girotra S, van Diepen S, Nallamothu BK, Carrel M, Vellano K, Anderson ML, et al. Regional Variation in Out-of-Hospital Cardiac Arrest Survival in the United States. Circulation. 2016;133:2159-68.
34. Ringh M, Jonsson M, Nordberg P, Fredman D, Hasselqvist-Ax I, Hakansson F, et al. Survival after Public Access Defibrillation in Stockholm, Sweden--A striking success. Resuscitation. 2015;91:1-7.
35. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, et al. Temperature Management After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association

Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation. 2016;98:97-104.

36. Kalra R, Arora G, Patel N, Doshi R, Berra L, Arora P, et al. Targeted Temperature Management After Cardiac Arrest: Systematic Review and Meta-analyses. Anesth Analg. 2018;126:867-75.
37. Schenone AL, Cohen A, Patarroyo G, Harper L, Wang X, Shishehbor MH, et al. Therapeutic hypothermia after cardiac arrest: A systematic review/meta-analysis exploring the impact of expanded criteria and targeted temperature. Resuscitation. 2016;108:102-10.
38. Wang CH, Huang CH, Chang WT, Tsai MS, Yu PH, Wu YW, et al. Outcomes of Adult In-Hospital Cardiac Arrest Treated with Targeted Temperature Management: A Retrospective Cohort Study. PLoS One. 2016;11:e0166148.
39. Chan PS, Berg RA, Tang Y, Curtis LH, Spertus JA, American Heart Association's Get With the Guidelines-Resuscitation I. Association Between Therapeutic Hypothermia and Survival After In-Hospital Cardiac Arrest. JAMA. 2016;316:1375-82.
40. Sunamura M, Ter Hoeve N, van den Berg-Emons RJG, Boersma E, van Domburg RT, Geleijnse ML. Cardiac rehabilitation in patients with acute coronary syndrome with primary percutaneous coronary intervention is associated with improved 10-year survival. Eur Heart J Qual Care Clin Outcomes. 2018;4:168-72.
41. de Vries H, Kemps HM, van Engen-Verheul MM, Kraaijenhagen RA, Peek N. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. Eur Heart J. 2015;36:1519-28.
42. Dumas F, Rea TD. Long-term prognosis following resuscitation from out-of-hospital cardiac arrest: role of aetiology and presenting arrest rhythm. Resuscitation. 2012;83:1001-5.

SUPPLEMENTARY MATERIAL

Table A | Definitions of variables, as described in the NICE registry

Cardiovascular insufficiency	Angina or symptoms at rest or during minimal effort, such as dressing and personal hygiene (New York Heart Association class IV).
COPD	Chronic condition in which pulmonary function swiftly deteriorates. The most important pathologies which fall into this category are chronic bronchitis, chronic bronchiolitis and emphysema.
Respiratory insufficiency	Chronic restrictive, obstructive or vascular conditions in the lungs resulting in very severe restriction of mobility, or registered chronic hypoxia, secondary polycythaemia, severe pulmonary hypertension (PAPsys > 40 mm Hg), or respiratory dependence (e.g. O2-dependent active respiratory conditions, sarcoidosis, interstitial fibrosis, tuberculosis, chronic obstructive pulmonary diseases).
Renal insufficiency	Raised serum creatinine > 177 umol/L (2.0 mg/dl) and renal insufficiency in the medical history (before the current hospital admission). Or if the patient has been receiving long-term haemodialysis or peritoneal dialysis prior to the current hospital admission.
Liver cirrhosis	Positive biopsy and documented portal hypertension, or there have been previous periods of high gastrointestinal bleeding as a result of portal hypertension, or there have been previous periods of hepatic failure, coma or encephalopathy (before the current hospital admission).
(Hematologic) malignancy Metastasised neoplasm Haematological malignancy	Metastases which have been diagnosed by clinical examination or confirmed by a pathology report or if there is Stage IV cancer (not solely regional lymph nodes). Malignant lymphoma, acute leukaemia or multiple myeloma. Chronic leukaemia is only scored if the patient is undergoing active treatment or if there is a relationship to the current condition.
Aids	HIV-positive and clinical complications such as pneumocystis carinii pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis of toxoplasma infection, or HIV-positive with CD4 < 200.
Immunologic insufficiency	Long term immunosuppressive therapy, or corticosteroid use (short term high and long term low dosages), or active chemotherapy or radiotherapy in the past year, or chemotherapy or radiotherapy for Hodgkin or non-Hodgkin lymphoma at any time for IC admission, or humoral or cellular deficiencies.
Dysrhythmia	If one of the next diagnosis is present in combination with hemodynamic instability in 24 hours before ICU admission: arrhythmia, paroxysmal tachycardia, atrial fibrillation with high ventricular response (≥120/minute), second-/third degree AV-block. Hemodynamic instability is defined as systolic blood pressure <90mmHg, heart frequency >140 beats per minute, or need for medical intervention such as inotropes/vasopressors, defibrillation, anti-arrhythmic medication or a pacemaker.
Mechanical ventilation	Use of a ventilator at the moment of IC admission or immediately (within 15 minutes) thereafter. An endotracheal tube is not necessarily required; also patients with CPAP via a mask are connected to the ventilator.
CVA	Cerebral embolism, occlusion, bleeding, or infarction at ICU admission or within 1 hour after ICU admission.

Intracranial mass	If an abscess, tumour, bleeding, or subdural contusion identified by CT/MRI and causes midline shift, obliteration/distortion of the cerebral ventricles, bleeding in cerebral ventricle/subarachnoid space, mass of >4cm or a contrast enhanced mass. If mass effect is present at least within 1 hour after ICU admission, a CT scan is not mandatory.
Gastro intestinal bleeding	Hematemesis or melaena.
Diabetes	Medication-dependent form of diabetes. This must have been diagnosed before the current IC admission.
AKI	Renal replacement therapy (during first 24 hours of ICU stay), or Serum creatinine level greater than 1.5 mg/100 ml (or 133µmol/l) during the previous 24 hours, associated with oliguria. Oliguria is defined as urine production ≤150 ml over a period of 8 consecutive hours. This oliguria cannot be caused by a missing or tight-fitting urine catheter or due to incontinence.
Infection	Confirmed infection upon admission or if infection is confirmed during the first 24 hours of IC treatment. Accepted confirmation of infection are culture results and Gram staining. Perioperative findings may qualify as evidence: for example faeces in the open peritoneal cavity with laparotomy scores 'yes'. It is therefore also possible to score "yes" on basis of a very strong suspicion of infection in radiology (e.g. new infiltrate) in conjunction with the clinic (e.g. purulent sputum and fever). Laboratory confirmation (including verbal or fax confirmation) must be obtained during the first 24 hours of admission. If the results are received after this, a 'no' must be scored. If perioperative findings are used, the procedure must have taken place either immediately prior to ICU admission or during the first 24 hours of ICU treatment. If radiological or other imaging material is used, the evidence must be undisputed.
Vasoactive medication	Continuous intravenous vasoactive medication for a minimum period of one hour during the first 24 hours of ICU admission.
Thrombolytic therapy	Patient has undergone thrombolytic therapy following an acute myocardial infarction in the 24 hours prior to ICU admission or during the first 24 hours of ICU admission. Examples of thrombolytic therapy are streptokinase, t-PA (Tissue plasminogen activator), and urokinase.

Appendix 1 - Multivariable model

The variables included in the model are: calendar year dummies (2010, 2011, 2012, 2013, 2014, 2015, and 2016), age (<40, 40-<50, 50-<55, 55-<60, 60-<65, 65-<70, 70-<80, 80-<90, ≥90), gender (male, female), BMI (<22.8, 22.8-<24.6, 24.6-<26.2, 26.2-<29.3, ≥29.3, missing), GCS (≤5, 6-14, 15, missing), renal insufficiency/dialysis (yes, no), COPD/chronic respiratory insufficiency (yes, no), cardiovascular insufficiency (yes, no), liver cirrhosis (yes, no), (haematologic) malignancy (yes, no), immunologic insufficiency (yes, no), and diagnoses within 24 hours of ICU admission (dysrhythmia (yes, no), mechanical ventilation (yes, no), CVA, (yes, no) intracranial mass (yes, no), gastrointestinal bleeding (yes, no), diabetes mellitus (yes, no))

R-code of model (2):

```
Fit1multi <- coxph(survobject_365d ~ kalenderjr0716_d2011 + kalenderjr0716_d2012
+ kalenderjr0716_d2013 + kalenderjr0716_d2014 + kalenderjr0716_d2015 + kalen-
derjr0716_d2016
+ fnice_agekl + genderd1 + fbmikl5 + fgcs_0kl3 + chr_renalinsuff_dialysis + copd_respinsuf
+ neoplasm_hem_malign + aids_imm_insuf + cirrhosis + cardio_vasc_insuf + dysrhytmia
+ mech_ventil_0 + cva  + intracran_mass + gastro_bleed + diabetes + frailty(hospnonum))
```

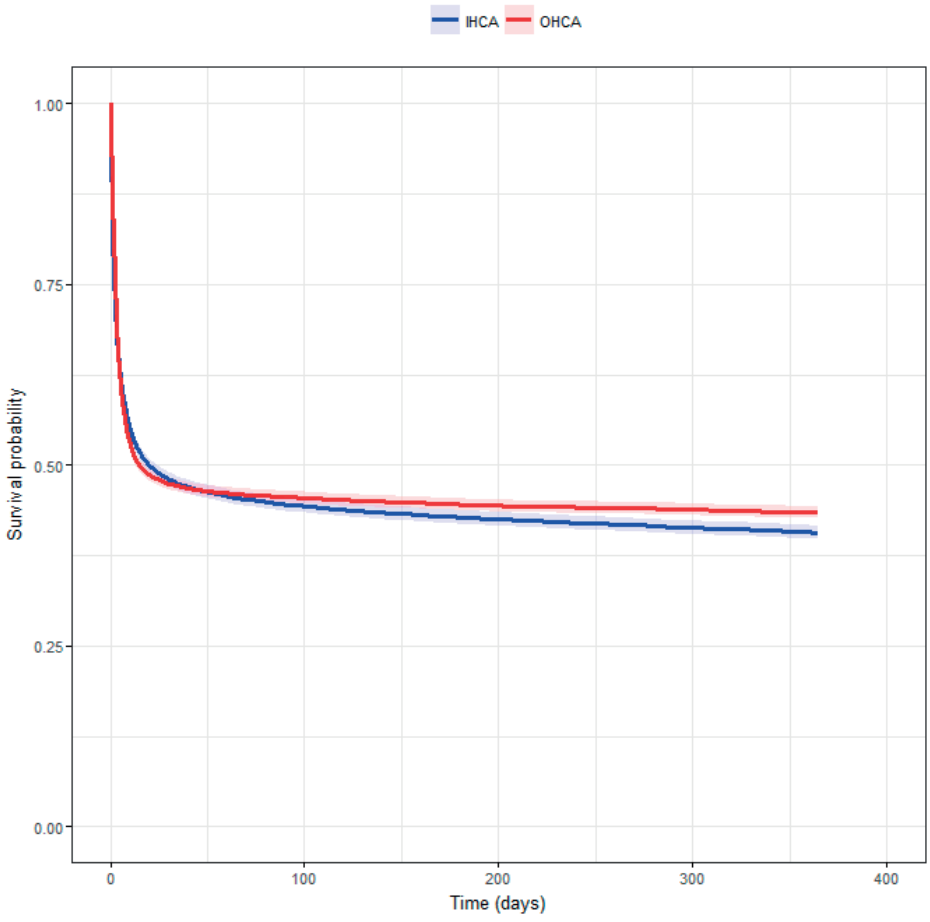


Figure A | Survival probability of IHCA and OHCA patients in the first year after CA

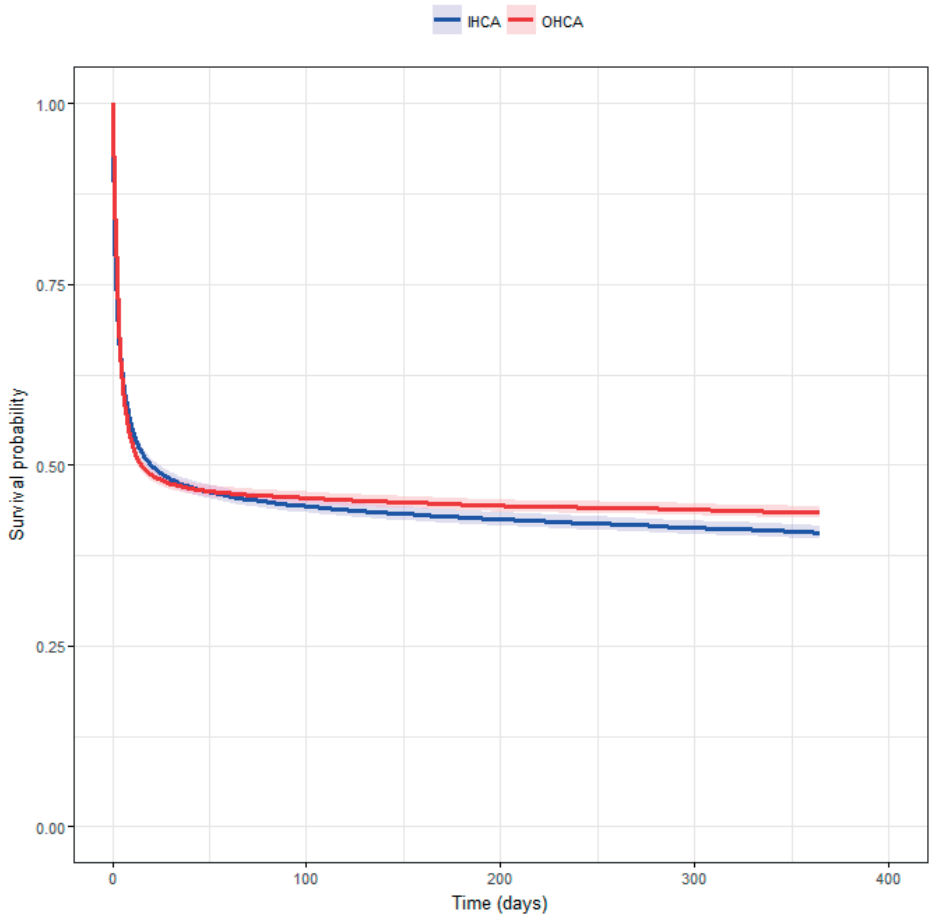


Figure B | Multivariable Cox-regression analysis of left truncated at hospital discharge data of 1-year mortality for OHCA over time (p<0.01).

Chapter 3

Higher 1-year mortality in women admitted to intensive care units after cardiac arrest: A nationwide overview from the Netherlands between 2010 and 2018

Loes Mandigers, Fabian Termorshuizen, Nicolette F. de Keizer, Wim Rietdijk, Diederik Gommers, Dinis dos Reis Miranda, Corstiaan A. den Uil

Journal of Critical Care; 64 (2021); 176–183

ABSTRACT

Purpose We study sex differences in 1-year mortality of out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) patients admitted to the intensive care unit (ICU).

Data A retrospective cohort analysis of OHCA and IHCA patients registered in the NICE registry in the Netherlands. The primary and secondary outcomes were 1-year and hospital mortality, respectively.

Results We included 19,440 OHCA patients (5977 women, 30.7%) and 13,461 IHCA patients (4889 women, 36.3%). For OHCA, 1-year mortality was 63.9% in women and 52.6% in men (Hazard Ratio [HR] 1.28, 95% Confidence Interval [95% CI] 1.23–1.34). For IHCA, 1-year mortality was 60.0% in women and 57.0% in men (HR 1.09, 95% CI 1.04–1.14). In OHCA, hospital mortality was 57.4% in women and 46.5% in men (Odds Ratio [OR]1.42, 95% CI 1.33–1.52). In IHCA, hospital mortality was 52.0% in women and 48.2% in men (OR 1.11, 95% CI 1.03–1.20).

Conclusion Women admitted to the ICU after cardiac arrest have a higher mortality rate than men. After left-truncation, we found that this sex difference persisted for OHCA. For IHCA we found that the effect of sex was mainly present in the initial phase after the cardiac arrest.

Keywords: Cardiac Arrest, Heart Arrest, Intensive Care Units, Sex differences, Mortality, 1-year mortality

INTRODUCTION

Despite the advances in prevention and treatment, cardiovascular diseases (CVDs) are still the number one cause of death worldwide. [1] Globally CVDs account for almost one third of the deaths and in Europe even half of the deaths are caused by CVDs. [1] Within the CVDs cardiac arrest has the highest mortality rate. The mortality rate after cardiac arrest varies between 58 and 61% for patients admitted alive to the hospital. [2,3] Even though there are many epidemiological studies in CVDs as well as in cardiac arrest, there are still many risk factors understudied.

One of the factors that has already been studied in CVDs but less in cardiac arrest is sex. Women with CVDs are older [4,5], have more cardiovascular risk factors [4,6-8], and present more often with atypical symptoms than men. [9] Recently, some studies have also shown the importance of sex differences in patient characteristics, pathophysiology, course, and outcome after cardiac arrest. [4,6-11] Similar to other CVDs, women are older and there is a difference in type and number of comorbidities. [12-21] When cardiac arrest occurs in women, the primary cardiac rhythm is less often shockable and women have a lower number of affected coronary arteries. [12,15,22,23] Women with cardiac arrest have significant higher short-term mortality, however these differences tend to disappear after adjustment for age and primary cardiac rhythm. [13,15,16,18,19,21,24]

A recent study in 5717 emergency medical services (EMS)-treated out of hospital cardiac arrest (OHCA) patients in the Netherlands has shown that women have a lower rate of primary shockable cardiac rhythm and receive bystander cardiopulmonary resuscitation (CPR) less frequently. [12] Women have a higher mortality to hospital discharge than men, however this effect disappeared in the subgroup of patients with primary shockable cardiac rhythms. [12] Therefore, the authors hypothesised that the disparity between women and men may be caused by a longer delay from arrest onset to recognition by bystanders, more rapid transition to non-shockable cardiac rhythms due to biological factors, or a combination of both. [12] The majority of the studies on sex differences in cardiac arrest are focussing on short-term mortality. However, data presenting longer-term mortality is lacking.

Recent studies, have also examined the mortality of in-hospital cardiac arrest (IHCA) patients in the Netherlands. [25-28] These studies note that there is scarce data available on long-term outcomes (and particularly 1-year mortality) of IHCA patients. [27] Furthermore, Schluep et al. found in their systematic review a 1-year survival of 13.4% in IHCA patients. However, this study included all IHCA patients, also patients that were not admitted to the intensive care unit (ICU). [28] This specific patient group, IHCA patients admitted to the ICU, is still an understudied group of which not much is known.

In order to contribute to existing knowledge on sex differences in outcomes of OHCA and IHCA patients, the purpose of this study was to examine the 1-year mortality

of OHCA and IHCA patients admitted to the ICU in the Netherlands. Patients with an OHCA or IHCA who are subsequently admitted to the ICU are an important group to study. Especially as these patients survived the first episode of cardiac arrest (CA) (i.e., CPR). However, they are prone to haemodynamic deterioration/instability, ischaemia/reperfusion injury, and neurological damage [25].This study is a first step in investigating possible sex differences in long-term mortality after ICU admission for both OHCA and IHCA patients.

MATERIALS AND METHODS

Population, setting, and design

In this retrospective cohort study, we used data that was partly reported in a previous study by our research group. [25] However, we expanded this dataset with two additional years and changed the primary focus of the analysis. Observational data of all ICU admitted patients in the Netherlands are collected in the National Intensive Care Evaluation (NICE) registry. This is a nationwide quality of care registry for ICUs in the Netherlands. In this registry data on demographics, physiological and diagnostic data, patient outcomes, and ICU characteristics are prospectively collected. We performed a retrospective analysis of the data, derived from approximately 85% of the ICU departments in 2010 to 100% of the ICU departments in 2018. [25]

All adult cardiac arrest patients admitted to the ICUs in the Netherlands between January 2010 and December 2018 were included. The Medical Ethics Committee of the Erasmus MC Rotterdam, the Netherlands (number MEC–2018-1228) and the Scientific Board of the NICE Foundation (number 2018–01) approved this study. The need for informed consent was waived.

Characteristics and clinical outcomes

The characteristics and clinical outcomes we collected are described before. [25] We included patient characteristics, admission characteristics, and clinical outcomes. In Supplementary Digital Content Table A, we provide a full list of the definitions of these characteristics and clinical outcomes included in the study.

We included all adult (≥18 years) patients registered with an admission diagnosis of CA or CPR. Next, we stratified the characteristics and clinical outcomes for OHCA and IHCA patients. However, OHCA and IHCA were not encoded in the NICE registry. Therefore, we defined OHCA as an admission diagnosis of CA or CPR, with an admission origin in the ED or home. IHCA was defined as an admission diagnosis of CA or CPR, with admission origin within the hospital, excluding the emergency department (ED). [25] The characteristics and outcomes were analysed for OHCA patients and IHCA patients

separately. Next, we stratified the data based on sex and compared characteristics and clinical outcomes of women and men.

Primary and secondary outcomes

For our primary outcome we will focus on 1-year mortality. We choose this as our primary outcome as a previous consensus stated that for large studies long-term outcomes are preferred. [29] In order to determine this primary outcome, 1-year mortality, we linked data from Vektis, an administrative database with claims of all insurance companies in the Netherlands. [30,31] Our secondary outcome is hospital mortality.

Statistical analysis

Descriptive statistics are reported as number (percentage, %) or median (interquartile range, IQR). To test for differences between women and men, we used Chi-square tests for categorical variables and Wilcoxon tests for continuous variables. To study the primary outcome, 1-year mortality, we performed multivariable Cox proportional hazard regressions comparing women and men, for OHCA and IHCA separately. The proportional hazard assumption in the Cox proportional hazard regressions may be violated as the effect of sex on the hazard of death is different for different intervals since ICU admission. In order to test this, we will repeat the Cox proportional hazard regressions with different left-truncation thresholds (i.e., hospital discharge, 30 days, 90 days, 180 days, and 270 days). The results of the Cox proportional hazard regressions are presented as Hazard Ratios (HR) and 95% confidence interval (95% CI).

To analyse the secondary outcome, hospital mortality, we performed a binary logistic regression comparing women and men for OHCA and IHCA separately. These results are presented as Odds Ratios (OR) and 95% CI. Both the Cox proportional hazard regression as well as the binary logistic regression were adjusted for age, body mass index [BMI], medical history (e.g., renal insufficiency/dialysis, chronic obstructive pulmonary disease [COPD]/ chronic respiratory insufficiency, cardiovascular insufficiency, liver cirrhosis, malignancy [including hematologic malignancies], immunologic insufficiency [including AIDS]), diagnosis on admission (i.e., mechanical ventilation, cerebrovascular accident [CVA], intracranial mass, gastro intestinal bleeding, and diabetes mellitus), and Glasgow Coma Scale (GCS). We included these admission characteristics as these are known at ICU admission and are relevant factors in explaining mortality. All analyses were performed using R-studio, version 3.6.1, and p-values <0.05 were considered statistically significant.

RESULTS

Of the total 689,289 patients included in the NICE registry between 2010 and 2018, 34,036 (4.9%) were admitted to the ICU due to CA. In 32,901 patients the location of arrest (OHCA or IHCA) could be determined and they were included in this study. 19,440 (59.1%) patients suffered from an OHCA, of which 5977 (30.8%) were women, and 13,461 (40.9%) patients suffered from an IHCA, of which 4889 (36.3%) were women.

Descriptive statistics

The descriptive statistics are presented in Table 1 showing the sex differences in patient characteristics and admission characteristics of OHCA patients and Table 2 showing the sex differences in patient characteristics and admission characteristics of IHCA patients. We also provide information about the number of missing values for each variable. As for the GCS at admission and 24 h after ICU admission were measured only in earlier years of the NICE registry. It was decided to stop collection of the GCS data in recent years. For this reason, the number of missing values is in these variables are large. Nevertheless, we decided to present the data that is available but not use GCS in our multivariable analysis.

Table 1 | Patient and admission characteristics for OHCA patients, for women and men

	Total	*Women*	*Men*	*p-value*	*Missing values (%)*
Patient characteristics					
Patient no	19,440	5977	13,463		
Age (IQR)	66 (55-75)	67 (54-76)	66 (56-74)	0.07	0 (0.0)
BMI (IQR)	25.8 (23.4-28.7)	25.7 (22.9-29.4)	26.0 (23.7-28.1)	0.03	1294 (6.7)
History					0 (0.0)
Cardiovascular insufficiency (%)	1297 (6.7)	322 (5.4)	975 (7.2)	<0.01	
COPD/respiratory insufficiency (%)	2731 (14.0)	1000 (16.7)	1731 (12.9)	<0.01	
Renal insufficiency (%)	1011 (5.2)	299 (5.0)	712 (5.3)	0.43	
Liver cirrhosis (%)	173 (0.9)	69 (1.2)	104 (0.8)	0.01	
Malignancy including hematological malignancy (%)	521 (2.7)	196 (3.3)	325 (2.4)	<0.01	
Immunodeficiency (%)	700 (3.6)	285 (4.8)	415 (3.1)	<0.01	
Admission characteristics					
APACHE IV estimated mortality rate (IQR)	0.8 (0.5-0.9)	0.8 (0.5-0.9)	0.8 (0.5-0.9)	1.00	80 (0.04)
Admission type				0.36	80 (0.04)

Table 1 | Patient and admission characteristics for OHCA patients, for women and men (*continued*)

	Total	*Women*	*Men*	*p-value*	*Missing values (%)*
Medical (%)	19,193 (99.1)	5896 (99.1)	13,297 (99.1)		
Urgent surgical (%)	158 (0.8)	42 (0.7)	116 (0.9)		
Elective surgical (%)	9 (<0.1)	4 (0.1)	5 (<0.1)		
GCS on admission				0.08	4836 (25.0)
GCS ≤ 5 (%)	10,454 (71.6)	3310 (72.8)	7144 (71.0)		
GCS 6-14 (%)	2260 (15.5)	670 (14.7)	1590 (15.8)		
GCS 15 (%)	1890 (12.9)	564 (12.4)	1326 (13.2)		
Diagnosis on admission					0 (0.0)
Mechanical ventilation (%)	17,711 (91.1)	5404 (90.4)	12,307 (91.4)	0.03	
CVA (%)	568 (2.9)	247 (4.1)	321 (2.4)	<0.01	
Intracranial mass (%)	434 (2.2)	199 (3.3)	235 (1.7)	<0.01	
Gastro intestinal bleeding (%)	291 (1.5)	103 (1.7)	188 (1.4)	0.10	
Diabetes Mellitus (%)	2976 (15.3)	1032 (17.3)	1944 (14.4)	<0.01	
GCS - At 24 hours after ICU admission				0.02	4864 (25.0)
GCS ≤ 5 (%)	8650 (59.3)	2755 (60.8)	5895 (58.7)		
GCS 6-14 (%)	2492 (17.1)	719 (15.9)	1773 (17.6)		
GCS 15 (%)	3434 (23.6)	1056 (23.3)	2378 (23.7)		
Diagnosis at 24h of ICU admission					0 (0.0)
AKI (%)	3082 (15.9)	994 (16.6)	2088 (15.5)	0.05	
Mechanical ventilation (%)	18,238 (93.8)	5576 (93.3)	12,662 (94.1)	<0.05	
Infection (%)	1481 (7.6)	520 (8.7)	961 (7.1)	<0.01	
Vasoactive medication (%)	14,526 (74.7)	4371 (73.1)	10,155 (75.4)	<0.01	
Thrombolytic therapy (%)	806 (4.1)	224 (3.7)	582 (4.3)	0.07	
Academic hospital (%)	5405 (27.8)	1576 (26.4)	3829 (28.4)	<0.01	0 (0.0)

OHCA: out-of-hospital cardiac arrest, BMI: body-mass index, COPD: chronic obstructive pulmonary disease, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, CVA: cerebrovascular accident, AKI: acute kidney injury

In OHCA patients, we found no statistically significant difference in age between women and men (67 years vs. 66 years, p= 0.07). Women had a lower incidence of prior cardiovascular insufficiency than men (5.4% vs. 7.2%, p< 0.01). A higher incidence of prior COPD/respiratory insufficiency was found in women (16.7%) than in men (12.9%, p< 0.01). At admission, women were more often known with diabetes mellitus than men (17.3% vs. 14.4%, p<0.01). Table 3 presents the clinical outcomes. Women had shorter length of ICU stay than men (4.2 days vs .6.2 days, p< 0.01).

Table 2 | Patient and admission characteristics for IHCA patients, for women and men

	Total	*Women*	*Men*	*p-value*	*Missing values (%)*
Patient characteristics					
Patient no	13,461	4889	8572		
Age (IQR)	69 (59-77)	70 (58-78)	68 (59-76)	<0.01	0 (0.0)
BMI (IQR)	25.8 (23.4-29.1)	25.7 (22.9-29.7)	25.8 (23.5-28.4)	0.94	849 (6.0)
History					0 (0.0)
Cardiovascular insufficiency (%)	1438 (10.7)	444 (9.1)	994 (11.6)	<0.01	
COPD /respiratory insufficiency (%)	2339 (17.4)	907 (18.6)	1432 (16.7)	<0.01	
Renal insufficiency (%)	1261 (9.4)	399 (8.2)	862 (10.1)	<0.01	
Liver cirrhosis (%)	178 (1.3)	61 (1.2)	117 (1.4)	0.62	
Malignancy including hematologic malignancies (%)	869 (6.5)	353 (7.2)	516 (6.0)	<0.01	
Immunodeficiency (%)	979 (7.3)	400 (8.2)	579 (6.8)	<0.01	
Admission characteristics					
APACHE IV estimated mortality rate (IQR)	0.7 (0.3-0.9)	0.7 (0.3-0.9)	0.7 (0.3-0.9)	<0.01	87 (0.65)
Admission type				0.02	54 (0.40)
Medical	10,113 (75.4)	3617 (74.3)	6496 (76.1)		
Urgent surgical	1957 (14.6)	725 (14.9)	1232 (14.4)		
Elective surgical	1337 (10.0)	528 (10.8)	809 (9.5)		
GCS on admission				0.87	2774 (21.0)
GCS ≤ 5 (%)	5479 (51.3)	2003 (51.4)	3479 (51.2)		
GCS 6-14 (%)	1794 (16.8)	645 (16.5)	1149 (16.9)		
GCS 15 (%)	3414 (31.9)	1251 (32.1)	2163 (31.9)		
Diagnosis on admission					0 (0.0)
Mechanical ventilation (%)	11,013 (81.8)	3928 (80.3)	7085 (82.7)	<0.01	
CVA (%)	464 (3.4)	178 (3.6)	286 (3.3)	0.38	
Intracranial mass (%)	269 (2.0)	114 (2.3)	155 (1.8)	0.04	
Gastro intestinal bleeding (%)	351 (2.6)	126 (2.6)	225 (2.6)	0.91	
Diabetes (%)	2563 (19.0)	972 (19.9)	1591 (18.6)	0.06	
GCS at 24h of ICU admission				0.1	2839 (21.0)
GCS ≤ 5 (%)	4735 (44.6)	1687 (43.6)	3048 (45.2)		
GCS 6-14 (%)	1658 (15.6)	592 (15.3)	1066 (15.8)		
GCS 15 (%)	4229 (39.8)	1594 (41.2)	2635 (39.0)		
Diagnosis at 24h of ICU admission					0 (0.0)
AKI (%)	2929 (21.8)	1028 (21.0)	1901 (22.2)	0.13	
Mechanical ventilation (%)	11,681 (86.8)	4184 (85.6)	7497 (87.5)	<0.01	
Infection (%)	2055 (15.3)	765 (15.6)	1290 (15.0)	0.37	

Table 2 | Patient and admission characteristics for IHCA patients, for women and men (*continued*)

	Total	*Women*	*Men*	*p-value*	*Missing values (%)*
Vasoactive medication (%)	9762 (72.5)	3457 (70.7)	6305 (73.6)	<0.01	
Thrombolytic therapy (%)	591 (4.4)	203 (4.2)	388 (4.5)	0.33	
Academic hospital (%)	3305 (24.6)	1132 (23.2)	2173 (25.3)	<0.01	0 (0.0)

OHCA: out-of-hospital cardiac arrest, BMI: body-mass index, COPD: chronic obstructive pulmonary disease, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, CVA: cerebrovascular accident, AKI: acute kidney injury

In IHCA patients, women had a higher median age than men (70 years vs. 68 years, p<0.01). As in OHCA patients, women who suffered IHCA had a lower incidence of prior cardiovascular insufficiency than men (9.1% vs. 11.6%, p< 0.01) and a higher incidence of prior COPD/respiratory insufficiency was found in women (18.6%) than in men (16.7%, p< 0.01). At admission, women received less often mechanical ventilation than men (85.6% vs. 87.5%, p< 0.01). Women had shorter length of ICU stay (5.3 days vs. 6.4 days, p< 0.01), as shown in Table 3.

Table 3 | Clinical outcomes for OHCA and IHCA patients, for women and men

	Total	*Women*	*Men*	*p-value*	*Missing values (%)*
OHCA					
Length of ICU stay in hours (IQR)	66.7 (25.2-127.7)	56.9 (19.4-118.4)	69.9 (29.5-132.9)	<0.01	0 (0.0)
Hospital length of stay in days (IQR)	5.5 (1.9-14.4)	4.2 (1.4-12.5)	6.2 (2.2-15.1)	<0.01	31 (0.2)
ICU mortality (%)	8814 (45.3)	3170 (53.0)	5644 (41.9)	<0.01	0 (0.0)
Hospital mortality (%)	9690 (49.8)	3432 (57.4)	6258 (46.5)	<0.01	0 (0.0)
1-year mortality (%)	10,909 (56.1)	3821 (63.9)	7088 (52.6)	<0.01	0 (0.0)
IHCA					
Length of ICU stay in hours (IQR)	50.5 (17.1-133.2)	45.9 (14.4-117.8)	54.9 (18.5-139.4)	<0.01	1 (0.01)
Hospital length of stay in days (IQR)	6.0 (1.5-15.1)	5.3 (1.3-14.1)	6.4 (1.7-15.6)	<0.01	27 (0.20)
ICU mortality (%)	5846 (43.4)	2256 (46.1)	3590 (41.9)	<0.01	0 (0.0)
Hospital mortality (%)	6670 (49.6)	2541 (52.0)	4129 (48.2)	<0.01	0 (0.0)
1-year mortality (%)	7823 (58.1)	2935 (60.0)	4888 (57.0)	<0.01	0 (0.0)

Primary outcome: 1-year mortality

In OHCA, women had a higher 1-year mortality than men (63.9% vs.52.6%, p < 0.01, Table 3). After adjustment in the Cox proportional hazard regression model this mortality difference remained statistically significant (HR 1.28, 95% CI 1.23–1.34, Table 4). Fig. 1 shows the Kaplan-Meier curve of 1-year mortality in OHCA patients. The Supplementary Digital Content Table B shows that the largest mortality difference between women and men in our study population is present in the initial phase after CA.

In IHCA, women had higher 1-year mortality than men (60.0% vs.57.0%, p<0.01, Table 3). After adjustment in the Cox proportional hazard regression model this mortality difference remained statistically significant (HR: 1.09, 95% CI 1.04–1.14, Table 4). Fig. 2 shows the Kaplan-Meier curve of 1-year mortality in IHCA patients. Likewise, the largest mortality difference between women and men in our study population is present in the initial phase after the cardiac arrest (4.2%, Supplementary Digital Content Table C).

Secondary outcome: hospital mortality

In OHCA patients, women had a higher hospital mortality than men (57.4% vs. 46.5%, p<0.01, Table 3). Supplementary Digital Content Table D shows that in the adjusted binary logistic regression model, this difference in hospital mortality remained statistically significant (OR 1.44, 95% CI 1.33–1.52).

In IHCA patients, women had a higher hospital mortality than men (52.0% vs. 48.2%, p < 0.01, Table 3). Supplementary Digital Content Table D shows that in the adjusted logistic regression model, this difference in hospital mortality remained statistically significant (OR 1.11, 95% CI 1.03–1.20).

Cox proportional hazard regression results

Table 4 presents the Cox proportional hazard regression results for OHCA and IHCA. Next to our estimates for sex differences we found some notable results. As for OHCA, we found that increasing age is positively associated with 1-year mortality. Further, we found that liver cirrhosis (HR 2.01, 95% CI 1.70–2.38) and intracranial mass (HR 3.06, 95% CI 2.73–3.44) are both positively associated with 1-year mortality. As for IHCA, we also found that increasing age is positively associated with 1-year mortality.

The proportional hazard assumptions

Table 5 presents the HRs for the left-truncation analysis. As for OHCA, the adjusted HR estimated with left-truncation at hospital discharge remains statistically significant and in the same magnitude as compared to no left-truncation (HR 1.37, 95% CI 1.25–1.49). Although the magnitude of the HRs are similar across the increasing left-truncation thresholds, the statistical significance over the truncation thresholds disappear. This is likely due to the decreasing sample size after left-truncation. For OHCA, we provide evi-

Table 4 | Multivariable Cox regression analysis for 1-year mortality in OHCA and IHCA patients

		OHCA	IHCA
Women		1.28 (1.23-1.34)	1.09 (1.04-1.14)
Age	<40	Reference	
	40-50	0.88 (0.79-0.98)	0.86 (0.74-1.01)
	50-55	0.89 (0.79-0.99)	1.04 (0.88-1.21)
	55-60	0.92 (0.83-1.03)	1.02 (0.88-1.19)
	60-65	1.04 (0.94-1.15)	1.16 (1.01-1.34)
	65-70	1.18 (1.07-1.30)	1.33 (1.16-1.53)
	70-80	1.44 (1.32-1.58)	1.57 (1.38-1.79)
	80-90	2.29 (2.08-2.52)	2.15 (1.88-2.46)
	>90	3.11 (2.64-3.66)	2.78 (2.25-3.45)
BMI	<20	1.11 (1.04-1.18)	1.12 (1.04-1.20)
	20-25	Reference	
	25-27.5	1.00 (0.97-1.10)	1.01 (0.94-1.09)
	27.5-30	0.95 (0.89-1.01)	0.91 (0.84-0.98)
	>30	1.04 (0.97-1.10)	0.97 (0.90-1.04)
Medical history	Cardiovascular insufficiency	1.01 (0.94-1.09)	1.17 (1.09-1.25)
	COPD /respiratory insufficiency	1.36 (1.30-1.43)	1.22 (1.15-1.29)
	Renal insufficiency	1.34 (1.24-1.45)	1.24 (1.15-1.33)
	Liver cirrhosis	2.01 (1.70-2.38)	1.55 (1.30-1.84)
	Malignancy including hematologic malignancies	1.86 (1.68-2.06)	1.78 (1.64-1.94)
	Immunodeficiency	1.12 (1.02-1.23)	1.25 (1.15-1.35)
Diagnosis on admission	Mechanical ventilation	1.27 (1.17-1.37)	1.25 (1.17-1.34)
	CVA	1.32 (1.19-1.48)	1.19 (1.06-1.35)
	Intracranial mass	3.06 (2.73-3.44)	1.55 (1.33-1.80)
	Gastro intestinal bleeding	1.50 (1.30-1.72)	1.53 (1.34-1.73)
	Diabetes Mellitus	1.24 (1.89-1.30)	1.15 (1.09-1.22)
GCS on admission	<5	2.18 (2.01-2.36)	2.61 (2.45-2.79)
	6-14	0.83 (0.75-0.92)	1.37 (1.26-1.49)
	15	Reference	
N		19,440	13,461
-2 Log likelihood		203,812.30	140,306.83
Likelihood ratio test p-value		<0.01	<0.01
AIC		203,868.30	140,362.83

Note: estimates are Hazard Ratios (HR) and 95% Confidence Interval (95% CI), derived from a Cox proportional hazard regression analysis. OHCA: out of hospital cardiac arrest, IHCA: in-hospital cardiac arrest, BMI: body mass index, CVA: cerebrovascular accident, GCS: Glasgow Coma Scale

Table 5 | Cox proportional hazard regressions for 1-year mortality at different left-truncation thresholds

OHCA			Women	Men
	Crude	Adjusted	N_{total} ($N_{non\text{-}survivors}$, % survival)	N_{total} ($N_{non\text{-}survivors,}$ % Survival)
No left truncation	1.39 [1.34-1.45]	1.28 [1.23-1.33]	5977 (3821, 64%)	13,463 (7088, 53%)
Left truncation at:				
At hospital discharge	1.51 [1.39-1.64]	1.37 [1.25-1.49]	3021 (879, 29%)	7975 (1636, 21%)
At 30 days	1.37 [1.17-1.59]	1.21 [1.04-1.42]	2390 (238, 10%)	6859 (506, 7%)
At 90 days	1.33 [1.08-1.63]	1.19 [0.96-1.47]	2257 (132, 6%)	6560 (290, 4%)
At 180 days	1.41 [1.06-1.87]	1.31 [0.98-1.76]	2160 (70, 3%)	6293 (146, 2%)
At 270 days	1.45 [0.98-2.16]	1.39 [0.93-2.08]	2079 (37, 2%)	6124 (75, 1%)
IHCA	Crude	Adjusted		
No left truncation	1.11 [1.06-1.16]	1.09 [1.04-1.14]	4889 (2935, 60%)	8572 (4888, 57%)
Left truncation at:				
At hospital discharge	0.99 [0.90-1.09]	0.97 [0.88-1.07]	2606 (668, 26%)	4904 (1256, 26%)
At 30 days	1.04 [0.91-1.19]	1.01 [0.88-1.15]	2277 (334, 15%)	4260 (598, 14%)
At 90 days	1.10 [0.92-1.33]	1.05 [0.87-1.27]	2086 (177, 8%)	3904 (300, 8%)
At 180 days	1.07 [0.82-1.38]	1.03 [0.79-1.36]	1952 (90, 5%)	3659 (158, 4%)
At 270 days	1.06 [0.72-1.55]	1.04 [0.70-1.55]	1847 (41, 2%)	3465 (73, 2%)

dence that the proportional hazard assumption holds. Supplementary Digital Content Fig. E shows the survival curves for OHCA patients when the increasing left-truncation thresholds are applied.

As for IHCA, the adjusted HRs estimated with left-truncation at the different thresholds are statistically insignificant and smaller as compared to no left-truncation. For IHCA, we found some evidence that the proportional hazard assumption is violated. Supplementary Digital Content Fig. F shows the survival curves for OHCA patients when the increasing left-truncation thresholds are applied.

DISCUSSION

This nationwide study showed that women who are admitted to the ICU after both OHCA and IHCA have a higher 1-year mortality than men. After left-truncation, for OHCA we found that the HRs remained relatively constant suggesting a persistent effect of sex on mortality during the first year after CA. At the same time for IHCA, after left-truncation, the effect of sex was mainly present in the initial phase after CA but decreases at later stages of follow-up. Our results suggests that the effect of sex on mortality during all intervals of the first year is more pronounced in OHCA than in IHCA patients.

Other studies comparing 1-year mortality in women and men in OHCA and IHCA are scarce and performed in smaller samples. McLaughlin et al. [32] investigated long-term mortality in hospital survivors of a combined sample of OHCA and IHCA patients (n= 1433). They found a significantly higher mortality rate in women (53%) than in men (43%, p< 0.01), at a median follow up of 3.6 years. [32] This effect disappeared after adjustment for baseline covariates including cardiac characteristics (HR 1.05, 95% CI 0.85–1.29). Wissenberg et al. [33] showed a significantly higher unadjusted mortality rate (p< 0.01) in EMS-treated OHCA in women than in men. These mortality rates are much higher than the mortality rates we found, which is probably due to the difference in included patients (EMS-treated versus ICU-admitted CA patients). Another study performed by Lindgren et al. [23] among 1498 OHCA patients showed no difference in 1-year mortality rate between women and men. We could not find studies comparing 1-year mortality in women and men only including IHCA patients. Schluep et al. [28] performed a meta-analysis and found an overall 1-year mortality of 82.4%, but these studies also included patients who died before ICU admission. A meta-analysis of Fennessy et al. [34] showed a very low overall 1-year mortality of 3.0–14.3%, however they only included hospital survivors. In another study performed by Schluep et al. [26] performed in a single centre a 1-year mortality of 74% was found in ICU admitted IHCA patients.

Our secondary outcome was hospital mortality, which we also found to be higher in women than in men in both OHCA and IHCA. Sex differences in hospital mortality have been described more often. John et al. [22] combined OHCA and IHCA patients and found equal hospital mortality rates in women (21%) and in men (23%, p= 0.68). Unfortunately, they did not stratify for OHCA/IHCA, their sample size was smaller, and was focussed on patients undergoing a coronary angiogram. Many recent studies in OHCA patients found a higher mortality in women in univariable analyses but not in multivariable analyses. [12,14,17,19,21,24,35] However, some studies did find a multivariable adjusted significantly higher mortality for women while correcting for cardiac characteristics, e.g., primary cardiac rhythm. [18,36,37] This disparity could be explained by cardiac factors in the causal pathway, which we could not adjust for. In our study hospital mortality rates in women after IHCA were higher than in men. Just few studies have been examining sex differences in IHCA patients. For example, Al Dury et al. [13] found higher mortality rates for women in their univariable analysis, but not in the multivariable analysis (OR 0.96, 95% CI 0.85–1.09). In a smaller study performed by Qvicket al. [38], no differences were shown in the univariable as well as the multivariable analysis. This could be due to the low proportions of women and men with shockable primary rhythm (18% vs. 21%, respectively).

It is not straightforward to explain the findings regarding sex differences in mortality after OHCA and IHCA of our study and recent literature. The differences in findings could be due to many factors, such as: heterogeneity of the aimed population, inclusion and

exclusion criteria, sample sizes, studied cardiac characteristics, awareness of bystanders, and prehospital, and in-hospital treatment differences between countries and hospitals. In most studies, primary cardiac rhythm seems to be an important contributing factor of the differences in mortality between women and men. Shockable primary cardiac rhythms are less often present in women than in men in both OHCA and IHCA. [12-21,24,33,37,38] A shockable primary cardiac rhythm is more often present in OHCA patients than in IHCA patients, and OHCA patients have higher probability of CA due to a cardiac aetiology than IHCA patients. [39-41] However, Sheak et al. [40] also found a higher probability of asystole as primary cardiac rhythm in OHCA patients than in IHCA patients. These authors did not present delay before start of CPR and occurrence of bystander CPR, which could have caused the shockable primary cardiac rhythms to be already converted to asystole. Finally, it may also be the case that there is some bias with respect to the treatment and care of women after cardiac arrest. Although, we attempted to include as much information about treatment, this should be confirmed in future studies.

Since the primary cardiac rhythm was not available in our study, we were not able to adjust for this factor. Therefore, we can only speculate if this is the only factor responsible for the sex differences that we found in both OHCA and IHCA. The general occurrence of a shockable primary cardiac rhythm and cardiac cause in IHCA is lower. Hence, the sex difference we found is most probably not only due to the primary cardiac rhythm. However, our results were indeed less pronounced in IHCA. With our results in mind, we hypothesise that despite the expected difference in primary cardiac rhythm and cause of arrest, the pathophysiology in women may also be different. The question investigating the cause of the sex difference would therefore be an important aim for future research. More detailed knowledge could result in a different approach and more specified treatment for women and men.

Limitations

We have previously discussed the limitations of the use of the NICE registry for studying CA. [25] For this study the most important limitation is the absence of cardiac characteristics, especially the unknown primary cardiac rhythm, the cause of CA, and time to ROSC. These factors may, at least in part, explain the observed differences. Other limitations include that, in the NICE registry, the location of arrest (OHCA or IHCA) is not registered. Therefore, we had to determine this with the best possible approximation using the admission origin. Next, we could only report mortality rates in this study, because there were no data available on neurological outcomes or quality of life after hospital discharge. Further, the statistically significant shorter length of stay we found in women is most probably due to the higher mortality in these patients. Finally, the increasing age of both OHCA and IHCA could influence the 1-year mortality. This mortality could

be caused by other age-related problems and not be a result of the CA. The mortality rates will probably be for some part overestimate the mortality caused by OHCA or IHCA.

CONCLUSION

Women admitted to the ICU after cardiac arrest have a higher mortality rate than men. After left-truncation, we found that this sex difference persisted for OHCA. For IHCA we found that the effect of sex was mainly present in the initial phase after the cardiac arrest.

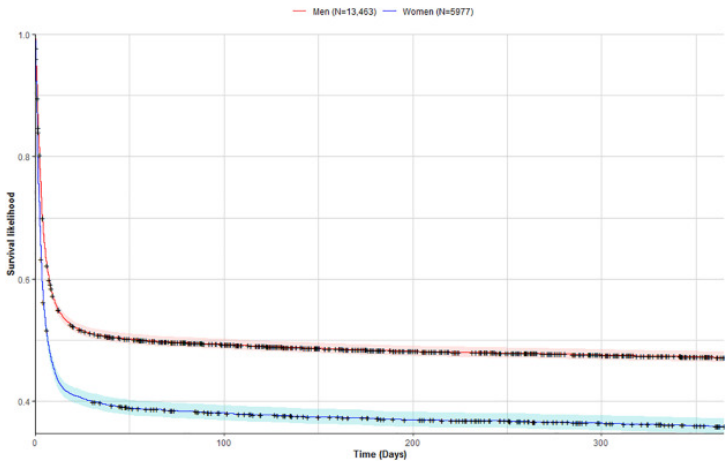


Figure 1 | 1-year mortality of women vs men in OHCA patients, Log-rank test $p < 0.01$.

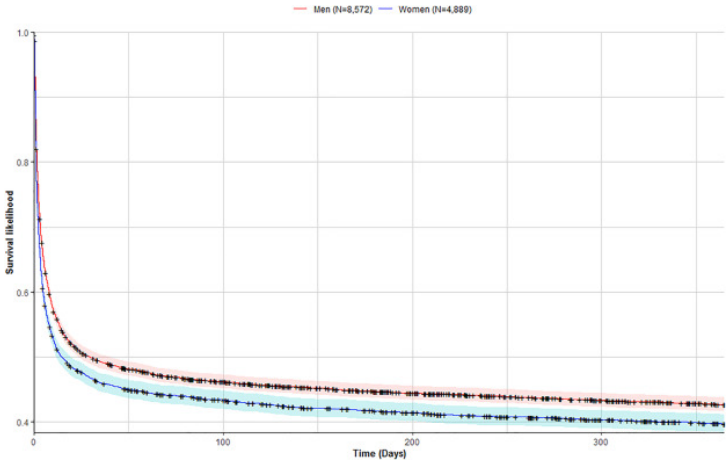


Figure 2 | 1-year mortality of women vs men in IHCA patients, Log-rank test $p < 0.01$.

REFERENCES

1. World Health Organisation. https://www.who.int/. 2020 [cited Available from: https://www.who.int/
2. Guterman EL, Kim AS, Josephson SA. Neurologic consultation and use of therapeutic hypothermia for cardiac arrest. Resuscitation 2017;118:43-48.
3. Kurz MC, Donnelly JP, Wang HE. Variations in survival after cardiac arrest among academic medical center-affiliated hospitals. PLoS One 2017;12(6):e0178793.
4. Wang Y, Zhu S, Du R, et al. Impact of gender on short-term and long-term all-cause mortality in patients with non-ST-segment elevation acute coronary syndromes: a meta-analysis. Intern Emerg Med 2018;13(2):273-285.
5. Zaman S, Deshmukh T, Aslam A, et al. Sex Differences in Electrophysiology, Ventricular Tachyarrhythmia, Cardiac Arrest and Sudden Cardiac Death Following Acute Myocardial Infarction. Heart Lung Circ 2020;29(7):1025-1031.
6. Bucholz EM, Butala NM, Rathore SS, et al. Sex differences in long-term mortality after myocardial infarction: a systematic review. Circulation 2014;130(9):757-767.
7. Clemmensen P, Roe MT, Hochman JS, et al. Long-term outcomes for women versus men with unstable angina/non-ST-segment elevation myocardial infarction managed medically without revascularization: insights from the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes trial. Am Heart J 2015;170(4):695-705 e695.
8. Hemal K, Pagidipati NJ, Coles A, et al. Sex Differences in Demographics, Risk Factors, Presentation, and Noninvasive Testing in Stable Outpatients With Suspected Coronary Artery Disease: Insights From the PROMISE Trial. JACC Cardiovasc Imaging 2016;9(4):337-346.
9. Dey S, Flather MD, Devlin G, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart 2009;95(1):20-26.
10. Akdis D, Saguner AM, Shah K, et al. Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome. Eur Heart J 2017;38(19):1498-1508.
11. Gudnadottir GS, Andersen K, Thrainsdottir IS, et al. Gender differences in coronary angiography, subsequent interventions, and outcomes among patients with acute coronary syndromes. Am Heart J 2017;191:65-74.
12. Blom MT, Oving I, Berdowski J, et al. Women have lower chances than men to be resuscitated and survive out-of-hospital cardiac arrest. Eur Heart J 2019;40(47):3824-3834.
13. Al-Dury N, Rawshani A, Israelsson J, et al. Characteristics and outcome among 14,933 adult cases of in-hospital cardiac arrest: A nationwide study with the emphasis on gender and age. Am J Emerg Med 2017;35(12):1839-1844.
14. Bosson N, Kaji AH, Fang A, et al. Sex Differences in Survival From Out-of-Hospital Cardiac Arrest in the Era of Regionalized Systems and Advanced Post-Resuscitation Care. J Am Heart Assoc 2016;5(9).
15. Bray JE, Stub D, Bernard S, et al. Exploring gender differences and the "oestrogen effect" in an Australian out-of-hospital cardiac arrest population. Resuscitation 2013;84(7):957-963.
16. Dicker B, Conaglen K, Howie G. Gender and survival from out-of-hospital cardiac arrest: a New Zealand registry study. Emerg Med J 2018;35(6):367-371.
17. Bougouin W, Dumas F, Marijon E, et al. Gender differences in early invasive strategy after cardiac arrest: Insights from the PROCAT registry. Resuscitation 2017;114:7-13.

18. Goto Y, Funada A, Maeda T, et al. Sex-specific differences in survival after out-of-hospital cardiac arrest: a nationwide, population-based observational study. Crit Care 2019;23(1):263.
19. Ng YY, Wah W, Liu N, et al. Associations between gender and cardiac arrest outcomes in Pan-Asian out-of-hospital cardiac arrest patients. Resuscitation 2016;102:116-121.
20. Safdar B, Stolz U, Stiell IG, et al. Differential survival for men and women from out-of-hospital cardiac arrest varies by age: results from the OPALS study. Acad Emerg Med 2014;21(12):1503-1511.
21. Winther-Jensen M, Hassager C, Kjaergaard J, et al. Women have a worse prognosis and undergo fewer coronary angiographies after out-of-hospital cardiac arrest than men. Eur Heart J Acute Cardiovasc Care 2018;7(5):414-422.
22. John J, Parikh PB, Thippeswamy G, et al. Sex-related disparities in obstructive coronary artery disease, percutaneous coronary intervention, and mortality in adults with cardiac arrest. Int J Cardiol 2018;269:23-26.
23. Lindgren E, Covaciu L, Smekal D, et al. Gender differences in utilization of coronary angiography and angiographic findings after out-of-hospital cardiac arrest: A registry study. Resuscitation 2019;143:189-195.
24. Awad E, Christenson J, Grunau B, et al. Sex differences in out-of-hospital cardiac arrest interventions within the province of British Columbia, Canada. Resuscitation 2020;148:128-134.
25. Mandigers L, Termorshuizen F, de Keizer NF, et al. A nationwide overview of 1-year mortality in cardiac arrest patients admitted to intensive care units in the Netherlands between 2010 and 2016. Resuscitation 2020;147:88-94.
26. Schluep M, Rijkenberg S, Stolker RJ, et al. One-year mortality of patients admitted to the intensive care unit after in-hospital cardiac arrest: a retrospective study. J Crit Care 2018;48:345-351.
27. Perriot S, Mathias A, Perriard G, et al. Human Induced Pluripotent Stem Cell-Derived Astrocytes Are Differentially Activated by Multiple Sclerosis-Associated Cytokines. Stem Cell Reports 2018;11(5):1199-1210.
28. Schluep M, Gravesteijn BY, Stolker RJ, et al. One-year survival after in-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation 2018;132:90-100.
29. Becker LB, Aufderheide TP, Geocadin RG, et al. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. Circulation 2011;124(19):2158-2177.
30. Karakus A, Haas LEM, Brinkman S, et al. Trends in short-term and 1-year mortality in very elderly intensive care patients in the Netherlands: a retrospective study from 2008 to 2014. Intensive Care Med 2017;43(10):1476-1484.
31. van de Klundert N, Holman R, Dongelmans DA, et al. Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol 2015;44(6):1850-1850h.
32. McLaughlin TJ, Jain SK, Voigt AH, et al. Comparison of Long-Term Survival Following Sudden Cardiac Arrest in Men Versus Women. Am J Cardiol 2019;124(3):362-366.
33. Wissenberg M, Hansen CM, Folke F, et al. Survival after out-of-hospital cardiac arrest in relation to sex: a nationwide registry-based study. Resuscitation 2014;85(9):1212-1218.
34. Fennessy G, Hilton A, Radford S, et al. The epidemiology of in-hospital cardiac arrests in Australia and New Zealand. Intern Med J 2016;46(10):1172-1181.
35. Morrison LJ, Schmicker RH, Weisfeldt ML, et al. Effect of gender on outcome of out of hospital cardiac arrest in the Resuscitation Outcomes Consortium. Resuscitation 2016;100:76-81.

36. Casey SD, Mumma BE. Sex, race, and insurance status differences in hospital treatment and outcomes following out-of-hospital cardiac arrest. Resuscitation 2018;126:125-129.
37. Karlsson V, Dankiewicz J, Nielsen N, et al. Association of gender to outcome after out-of-hospital cardiac arrest--a report from the International Cardiac Arrest Registry. Crit Care 2015;19:182.
38. Qvick A, Radif M, Brever C, et al. Survival of in-hospital cardiac arrest in men and women in a large Swedish cohort. Scand J Trauma Resusc Emerg Med 2018;26(1):108.
39. Engsig M, Soholm H, Folke F, et al. Similar long-term survival of consecutive in-hospital and out-of-hospital cardiac arrest patients treated with targeted temperature management. Clin Epidemiol 2016;8:761-768.
40. Sheak KR, Wiebe DJ, Leary M, et al. Quantitative relationship between end-tidal carbon dioxide and CPR quality during both in-hospital and out-of-hospital cardiac arrest. Resuscitation 2015;89:149-154.
41. Wibrandt I, Norsted K, Schmidt H, et al. Predictors for outcome among cardiac arrest patients: the importance of initial cardiac arrest rhythm versus time to return of spontaneous circulation, a retrospective cohort study. BMC Emerg Med 2015;15:3.

SUPPLEMENTARY MATERIAL

Table A | Summary of variables and their definitions, as described in the NICE registry

Patient characteristics: sex, age, body mass index (BMI), and history (cardiovascular insufficiency, chronic obstructive pulmonary disease (COPD), respiratory insufficiency, renal insufficiency, liver cirrhosis, malignancy (including hematologic malignancy), aids, immunologic insufficiency).

Admission characteristics: Acute Physiology and Chronic Health Evaluation (APACHE IV) estimated mortality rate, admission type (medical, urgent surgical, elective surgical), diagnosis on admission (Glasgow Coma Scale [GCS], the use of mechanical ventilation, cerebrovascular accident [CVA], intracranial mass, gastro-intestinal bleeding, diabetes mellitus), and diagnoses within 24 hours of ICU admission (GCS, acute kidney injury [AKI], the use of mechanical ventilation, infection, vasoactive medication use, the administration of thrombolytic therapy, and admission at academic/non-academic hospital.

Clinical outcomes: length of stay at the Intensive Care Unit (ICU), length of stay at the hospital, ICU mortality, hospital mortality, and 1-year mortality.

Definitions of variables:

Cardiovascular insufficiency	Angina or symptoms at rest or during minimal effort, such as dressing and personal hygiene (New York Heart Association class IV).
COPD	Chronic condition in which pulmonary function swiftly deteriorates. The most important pathologies which fall into this category are chronic bronchitis, chronic bronchiolitis and emphysema.
Respiratory insufficiency	Chronic restrictive, obstructive or vascular conditions in the lungs resulting in very severe restriction of mobility, or registered chronic hypoxia, secondary polycythaemia, severe pulmonary hypertension (PAPsys > 40 mm Hg), or respiratory dependence (e.g. O2-dependent active respiratory conditions, sarcoidosis, interstitial fibrosis, tuberculosis, chronic obstructive pulmonary diseases).
Renal insufficiency	Raised serum creatinine > 177 umol/L (2.0 mg/dl) and renal insufficiency in the medical history (before the current hospital admission). Or if the patient has been receiving long-term haemodialysis or peritoneal dialysis prior to the current hospital admission.
Liver cirrhosis	Positive biopsy and documented portal hypertension, or there have been previous periods of high gastrointestinal bleeding as a result of portal hypertension, or there have been previous periods of hepatic failure, coma or encephalopathy (before the current hospital admission).
Malignancy (including hematologic malignancy) Metastasised neoplasm	Metastases which have been diagnosed by clinical examination or confirmed by a pathology report or if there is Stage IV cancer (not solely regional lymph nodes).
Haematological malignancy	Malignant lymphoma, acute leukaemia or multiple myeloma. Chronic leukaemia is only scored if the patient is undergoing active treatment or if there is a relationship to the current condition.
Aids	HIV-positive and clinical complications such as pneumocystis carinii pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis of toxoplasma infection, or HIV-positive with CD4 < 200.
Immunologic insufficiency	Long term immunosuppressive therapy, or corticosteroid use (short term high and long term low dosages), or active chemotherapy or radiotherapy in the past year, or chemotherapy or radiotherapy for Hodgkin or non-Hodgkin lymphoma at any time for IC admission, or humoral or cellular deficiencies.
Mechanical ventilation	Use of a ventilator at the moment of IC admission or immediately (within 15 minutes) thereafter. An endotracheal tube is not necessarily required; also patients with CPAP via a mask are connected to the ventilator.

Table A | Summary of variables and their definitions, as described in the NICE registry (*continued*)

Cardiovascular insufficiency	Angina or symptoms at rest or during minimal effort, such as dressing and personal hygiene (New York Heart Association class IV).
CVA	Cerebral embolism, occlusion, bleeding, or infarction at ICU admission or within 1 hour after ICU admission.
Intracranial mass	If an abscess, tumour, bleeding, or subdural contusion identified by CT/MRI and causes midline shift, obliteration/distortion of the cerebral ventricles, bleeding in cerebral ventricle/subarachnoid space, mass of >4cm or a contrast enhanced mass. If mass effect is present at least within 1 hour after ICU admission, a CT scan is not mandatory.
Gastro intestinal bleeding	Hematemesis or melaena.
Diabetes	Medication-dependent form of diabetes. This must have been diagnosed before the current IC admission.
AKI	Renal replacement therapy (during first 24 hours of ICU stay), or Serum creatinine level greater than 1.5 mg/100 ml (or 133µmol/l) during the previous 24 hours, associated with oliguria. Oliguria is defined as urine production ≤150 ml over a period of 8 consecutive hours. This oliguria cannot be caused by a missing or tight-fitting urine catheter or due to incontinence.
Infection	Confirmed infection upon admission or if infection is confirmed during the first 24 hours of IC treatment. Accepted confirmation of infection are culture results and Gram staining. Perioperative findings may qualify as evidence: for example faeces in the open peritoneal cavity with laparotomy scores 'yes'. It is therefore also possible to score "yes" on basis of a very strong suspicion of infection in radiology (e.g. new infiltrate) in conjunction with the clinic (e.g. purulent sputum and fever). Laboratory confirmation (including verbal or fax confirmation) must be obtained during the first 24 hours of admission. If the results are received after this, a 'no' must be scored. If perioperative findings are used, the procedure must have taken place either immediately prior to ICU admission or during the first 24 hours of ICU treatment. If radiological or other imaging material is used, the evidence must be undisputed.
Vasoactive medication	Continuous intravenous vasoactive medication for a minimum period of one hour during the first 24 hours of ICU admission.
Thrombolytic therapy	Patient has undergone thrombolytic therapy following an acute myocardial infarction in the 24 hours prior to ICU admission or during the first 24 hours of ICU admission. Examples of thrombolytic therapy are streptokinase, t-PA (Tissue plasminogen activator), and urokinase.

Table B | Differences in ICU length of stay and mortality between women and men in ICU survivors and hospital survivors of OHCA patients

	Women	*Men*	*Mortality difference*
Total OHCA patients	5977	13,463	NA
ICU length of stay in ICU survivors (in hours)	76.8 [38.3-162.3]	85.9 [45.4-158.8]	NA
ICU length of stay in ICU non-survivors (in hours)	41.9 [9.8-84.1]	51 [13.9-98.1]	NA
ICU mortality	3170 (53)	5644 (41.9)	11.1%
Hospital mortality in ICU survivors	262/2807= 9.3%	614 / 7819 = 7.9%	1.4%
1-year mortality in hospital survivors	389/2545 = 15.3%	830 / 7205 = 11.5%	3.8%

OHCA: out-of-hospital cardiac arrest, ICU: intensive care unit

Table C | Differences in ICU length of stay and mortality between women and men in ICU survivors and hospital survivors of IHCA patients

	Women	*Men*	*Mortality difference*
Total IHCA patients	4889	8572	NA
ICU length of stay in ICU survivors (in hours)	68.5 [25-158.8]	73.3 [26-165.5]	NA
ICU length of stay in ICU non-survivors (in hours)	22.5 [4.2-75.1]	32.4 [5.8-95.3]	NA
ICU mortality	2256 (46.1)	3590 (41.9)	4.2%
Hospital mortality in ICU survivors	285/2633 = 10.8%	539/4982 = 10.8%	0%
1-year mortality in hospital survivors	394/2348 = 16.8%	759/4443 = 17.1%	0.3%

IHCA: in-hospital cardiac arrest, ICU: intensive care unit

Table D | Multivariable logistic regression analysis for hospital mortality for OHCA and IHCA

		OHCA	IHCA
Women		1.42 (1.33-1.52)	1.11 (1.03-1.20)
Age	<40	Reference	Reference
	40-50	0.81 (0.69-0.95)	0.83 (0.66-1.04)
	50-55	0.79 (0.67-0.93)	1.01 (0.80-1.28)
	55-60	0.86 (0.74-1.01)	0.99 (0.80-1.24)
	60-65	1.01 (0.87-1.18)	1.13 (0.92-1.40)
	65-70	1.18 (1.02-1.37)	1.35 (1.11-1.66)
	70-80	1.57 (1.37-1.81)	1.75 (1.44-2.11)
	80-90	3.38 (2.90-3.94)	2.84 (2.32-3.49)
	>90	4.71 (3.33-6.66)	3.66 (2.47-5.43)
BMI	<20	1.12 (1.01-1.25)	1.22 (1.07-1.37)
	20-25	Reference	Reference
	25-27.5	0.99 (0.90-1.10)	1.10 (0.97-1.25)
	27.5-30	0.93 (0.84-1.03)	0.89 (0.79-1.01)
	>30	1.08 (0.98-1.20)	1.04 (0.93-1.18)
Medical history	Cardiovascular insufficiency	1.10 (0.97-1.25)	1.27 (1.12-1.43)
	COPD/respiratory insufficiency	1.72 (1.57-1.88)	1.50 (1.35-1.65)
	Renal insufficiency	1.62 (1.39-1.87)	1.35 (1.18-1.54)
	Liver cirrhosis	3.44 (2.36-5.01)	2.60 (1.84-3.69)
	Malignancy including hematological malignancies	2.36 (1.91-2.91)	2.28 (1.93-2.69)
	Immunodeficiency	1.33 (1.12-1.58)	1.53 (1.32-1.79)
Diagnosis *on admission*	Mechanical ventilation	1.65 (1.47-1.85)	1.67 (1.51-1.85)
	CVA	1.59 (1.28-1.97)	1.34 (1.08-1.68)
	Intracranial mass	4.54 (3.44-5.99)	2.00 (1.48-2.70)
	Gastro intestinal bleeding	2.26 (1.72-2.97)	2.00 (1.57-2.55)
	Diabetes	1.44 (1.31-1.57)	1.23 (1.11-1.36)
GCS *on admission*	<5	3.59 (3.20-4.04)	4.46 (4.04-4.92)
	6-14	0.83 (0.72-0.96)	1.50 (1.32-1.70)
	15	Reference	Reference
N		19,440	13,461
-2 Loglikelihood		23,716.65	16,424.44
Wald-test, p-value		<0.01	<0.01
AIC		23,774.65	16,482.44

Note: estimates are Odds Ratios (OR) and 95% Confidence Interval (95% CI), derived from a binary logistic regression analysis. OHCA: out-of-hospital cardiac arrest, IHCA: in-hospital cardiac arrest, BMI: body-mass index, CVA: cerebrovascular accident, GCS: Glasgow Coma Scale

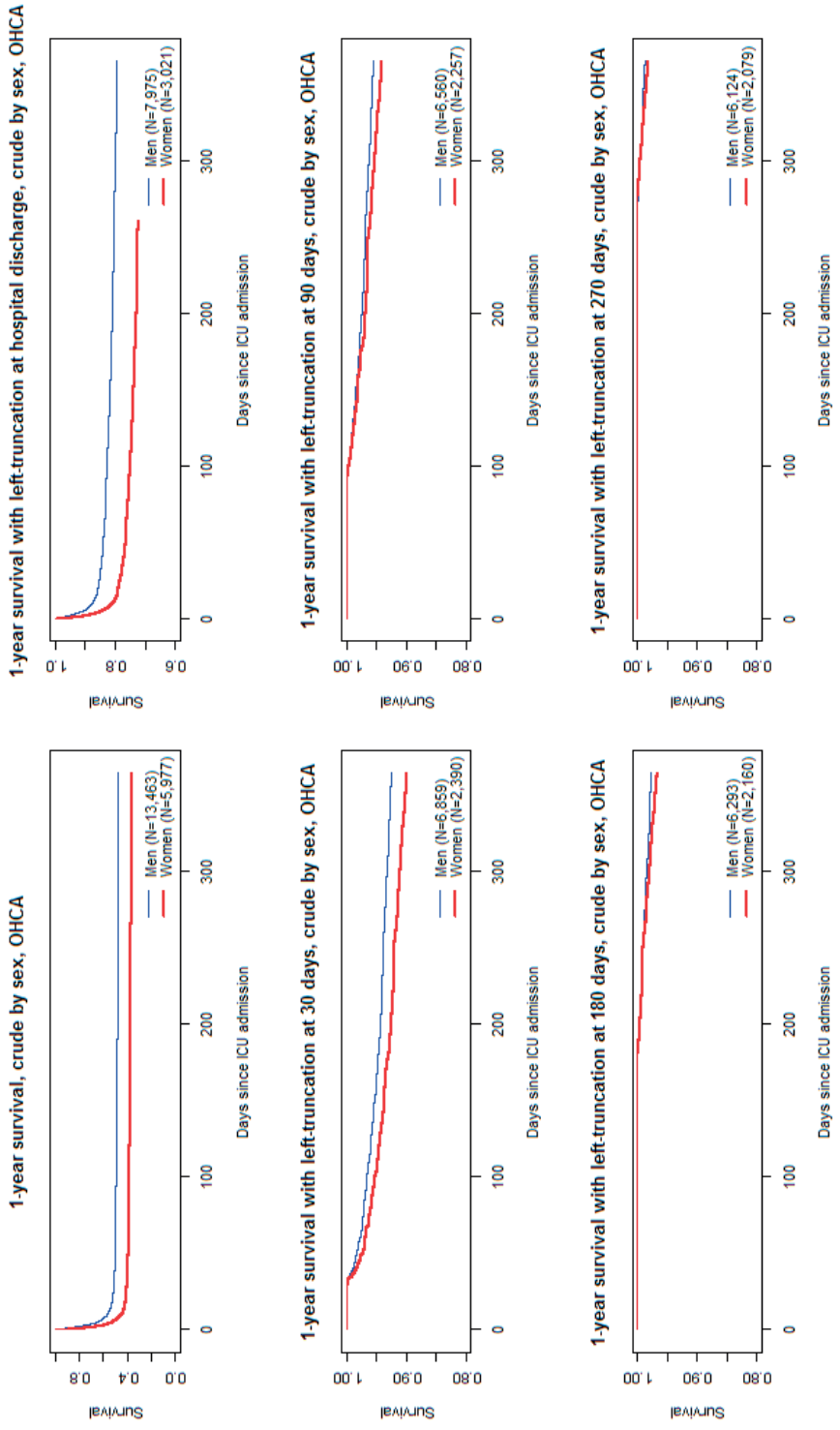


Figure E | Survival curves for OHCA patients at different left-truncation thresholds

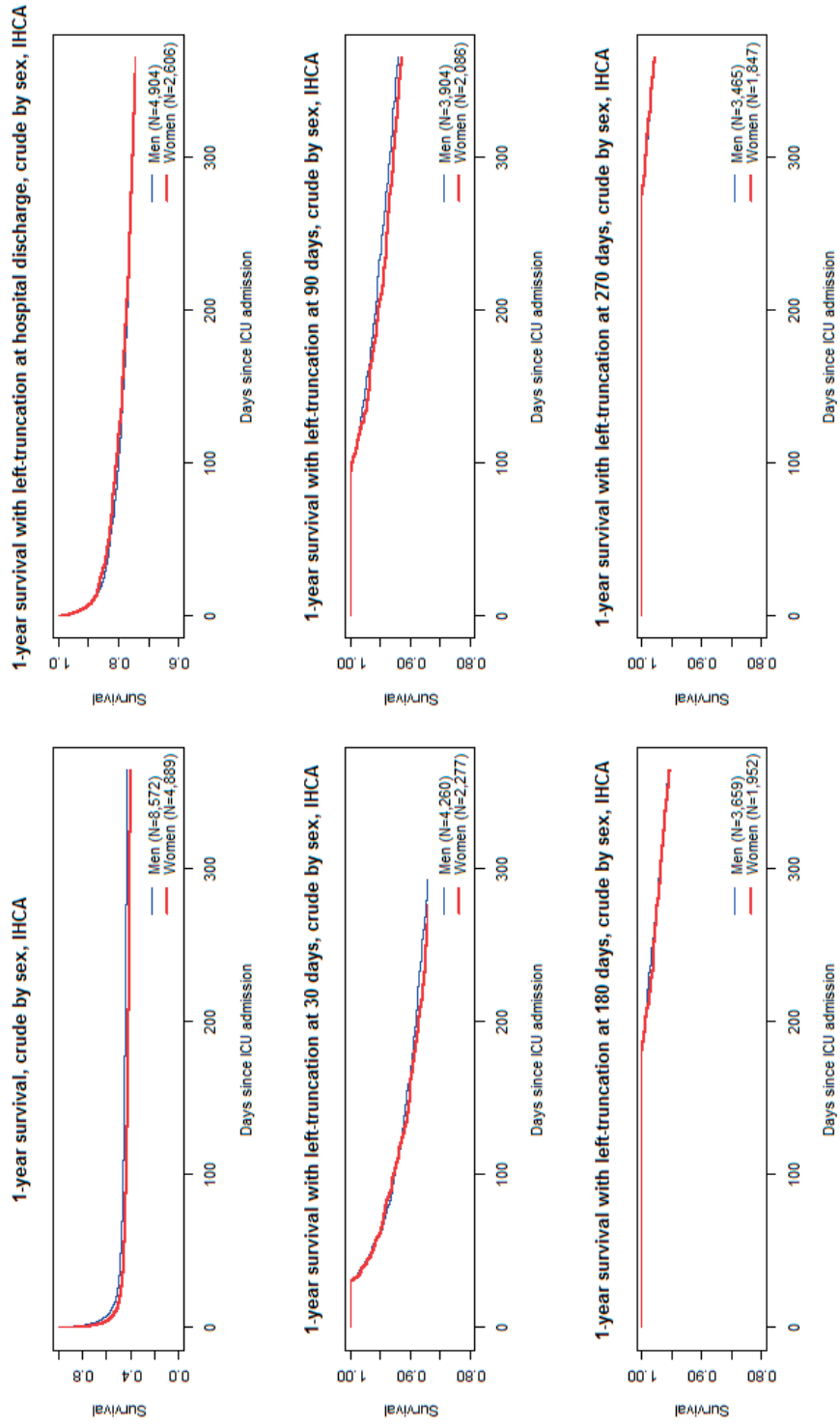


Figure F | Survival curves for IHCA patients at different left-truncation thresholds.

Table G | Number of missing values for women and men separately in the OHCA sample.

	Missing values (%)	
	Women	***Men***
Patient characteristics		
Patient no	5977	13,463
Age (%)	0 (0.0)	0 (0.0)
BMI (%)	423 (7.0)	871 (6.0)
History	0 (0.0)	0 (0.0)
Cardiovascular insufficiency (%)	0 (0.0)	0 (0.0)
COPD/respiratory insufficiency (%)	0 (0.0)	0 (0.0)
Renal insufficiency (%)	0 (0.0)	0 (0.0)
Liver cirrhosis (%)	0 (0.0)	0 (0.0)
Malignancy including hematological malignancy (%)	0 (0.0)	0 (0.0)
Immunodeficiency (%)	0 (0.0)	0 (0.0)
Admission characteristics		
APACHE IV estimated mortality rate (IQR)	32 (1.0)	48 (0.4)
Admission type	35 (0.6)	45 (0.3)
GCS at admission	1433 (24.0)	3403 (25.0)
Diagnosis on admission	0 (0.0)	0 (0.0)
Mechanical ventilation (%)	0 (0.0)	0 (0.0)
CVA (%)	0 (0.0)	0 (0.0)
Intracranial mass (%)	0 (0.0)	0 (0.0)
Gastro intestinal bleeding (%)	0 (0.0)	0 (0.0)
Diabetes Mellitus (%)	0 (0.0)	0 (0.0)

	Women	***Men***
GCS - At 24 hours after ICU admission	1447 (24.2)	3417 (25.4)
Diagnosis at 24h of ICU admission	0 (0.0)	0 (0.0)
AKI (%)	0 (0.0)	0 (0.0)
Mechanical ventilation (%)	0 (0.0)	0 (0.0)
Infection (%)	0 (0.0)	0 (0.0)
Vasoactive medication (%)	0 (0.0)	0 (0.0)
Thrombolytic therapy (%)	0 (0.0)	0 (0.0)
Academic hospital (%)	0 (0.0)	0 (0.0)

OHCA: out-of-hospital cardiac arrest, BMI: body-mass index, COPD: chronic obstructive pulmonary disease, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, CVA: cerebrovascular accident, AKI: acute kidney injury.

Table H | Number of missing values for women and men separately in the IHCA sample.

	Missing values (%)	
	Women	***Men***
Patient characteristics		
Patient no	4889	8572
Age (%)	0 (0.0)	0 (0.0)
BMI (%)	314 (6.4)	535 (6.2)
History	0 (0.0)	0 (0.0)
Cardiovascular insufficiency (%)	0 (0.0)	0 (0.0)
COPD/respiratory insufficiency (%)	0 (0.0)	0 (0.0)
Renal insufficiency (%)	0 (0.0)	0 (0.0)
Liver cirrhosis (%)	0 (0.0)	0 (0.0)
Malignancy including hematological malignancy (%)	0 (0.0)	0 (0.0)
Immunodeficiency (%)	0 (0.0)	0 (0.0)
Admission characteristics		
APACHE IV estimated mortality rate (IQR)	36 (0.7)	51 (0.6)
Admission type	19 (0.4)	35 (0.4)
GCS at admission	990 (20.2)	1784 (20.8)
Diagnosis on admission	0 (0.0)	0 (0.0)
Mechanical ventilation (%)	0 (0.0)	0 (0.0)
CVA (%)	0 (0.0)	0 (0.0)
Intracranial mass (%)	0 (0.0)	0 (0.0)
Gastro intestinal bleeding (%)	0 (0.0)	0 (0.0)
Diabetes Mellitus (%)	0 (0.0)	0 (0.0)

	Women	***Men***
GCS - At 24 hours after ICU admission	1016 (20.7)	1823 (21.3)
Diagnosis at 24h of ICU admission	0 (0.0)	0 (0.0)
AKI (%)	0 (0.0)	0 (0.0)
Mechanical ventilation (%)	0 (0.0)	0 (0.0)
Infection (%)	0 (0.0)	0 (0.0)
Vasoactive medication (%)	0 (0.0)	0 (0.0)
Thrombolytic therapy (%)	0 (0.0)	0 (0.0)
Academic hospital (%)	0 (0.0)	0 (0.0)

OHCA: out-of-hospital cardiac arrest, BMI: body-mass index, COPD: chronic obstructive pulmonary disease, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale, CVA: cerebrovascular accident, AKI: acute kidney injury.

Table I | Number of women and men per variable group in the regressions.

		OHCA		IHCA	
		Women	Men	Women	Men
Age	<40	765 (5.7)	456 (7.6)	255 (5.2)	330 (3.8)
	40-50	1186 (8.8)	601 (10.1)	386 (7.9)	563 (6.6)
	50-55	1131 (8.4)	501 (8.4)	305 (6.2)	507 (5.9)
	55-60	1370 (10.2)	521 (8.7)	364 (7.4)	792 (9.2)
	60-65	1665 (12.4)	609 (10.2)	499 (10.2)	1019 (11.9)
	65-70	2052 (15.2)	773 (12.9)	635 (13.0)	1401 (16.3)
	70-80	3587 (26.6)	1489 (24.9)	1412 (28.9)	2744 (32.0)
	80-90	1595 (11.8)	913 (15.3)	936 (19.1)	1155 (13.5)
	>90	113 (0.8)	114 (1.9)	97 (2.0)	61 (0.7)
BMI	<20	1855 (13.8)	1373 (23.0)	1142 (23.4)	1360 (15.9)
	20-25	2385 (17.7)	964 (16.1)	789 (16.1)	1573 (18.4)
	25-27.5	2977 (22.1)	803 (13.4)	594 (12.1)	1663 (19.4)
	27.5-30	2979 (22.1)	909 (15.2)	767 (15.7)	1812 (21.1)
	>30	2396 (17.8)	1505 (25.2)	1283 (26.2)	1629 (19.0)
	Missing*	871 (6.5)	423 (7.1)	314 (6.4)	535 (6.2)
GCS on admission	<5	7144 (53.1)	3310 (55.4)	2003 (41.0)	3476 (40.6)
	6-14	1590 (11.8)	670 (11.2)	645 (13.2)	1149 (13.4)
	>15	1326 (9.8)	564 (9.4)	1251 (25.6)	2163 (25.2)
	Missing values*	3403 (25.3)	1433 (24.0)	990 (20.2)	1784 (20.8)

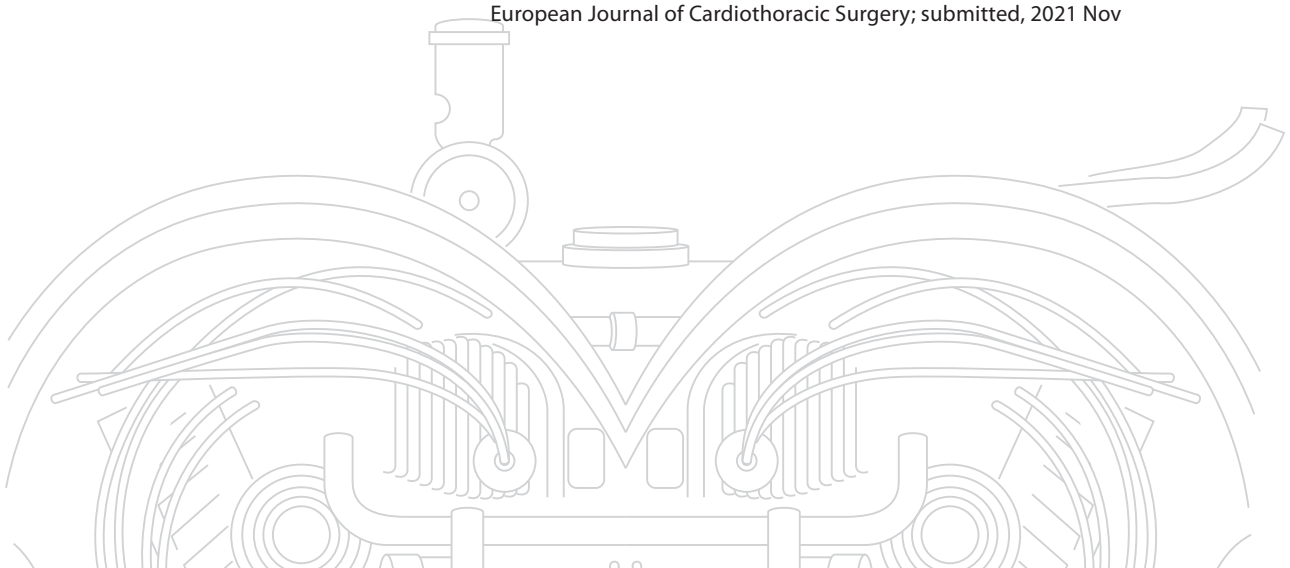
*Patients missing these values were included in the analysis as a separate category, but these estimates were not shown in table 4.

Chapter 4

Systematic review comparing low-flow duration of extracorporeal and conventional cardiopulmonary resuscitation

Loes Mandigers, Eric Boersma, Corstiaan A. den Uil, Diederik Gommers, Jan Bělohlávek, Mirko Belliato, Roberto Lorusso, Dinis dos Reis Miranda, on behalf of the EuroELSO working group on ECPR

European Journal of Cardiothoracic Surgery; submitted, 2021 Nov



ABSTRACT

Objective After cardiac arrest, a key factor determining survival outcomes is low-flow duration. This low-flow duration is defined as the time from start of cardiopulmonary resuscitation (CPR), until: return of spontaneous circulation, return of circulation using extracorporeal cardiopulmonary resuscitation (ECPR), or death. Our aims were to determine the relation of survival and low-flow duration of both ECPR and conventional CPR (CCPR) and if ECPR and CCPR have different short term survival curves in relation to low-flow duration.

Methods We searched Embase, Medline, Web of Science, and Google Scholar from inception up to April 2021. We included 42 observational studies reporting on 1,689 ECPR and 375,751 CCPR procedures. A linear mixed effect model was used to describe the course of survival over time, based on study-specific and time-specific aggregated survival data

Results Of the included studies, 25 included adults, 13 included children, and four included both. In adults, survival curves decline rapidly over time (ECPR 37.2%-29.8%-23.8%-19.1% versus CCPR-shockable 36.8%-7.2%-1.4%-0.3% for 15-30-45-60 minutes low-flow, respectively). ECPR was associated with a statistically significant slower decline in survival than CCPR with initial shockable rhythms (CCPR-shockable). In children, survival curves decline rapidly over time (ECPR 43.6%-41.7%-39.8%-38.0% versus CCPR-shockable 48.6%-20.5%-8.6%-3.6% for 15-30-45-60 minutes low-flow, respectively). ECPR was associated with a statistically significant slower decline in survival than CCPR-shockable.

Conclusions The short-term survival of ECPR and CCPR-shockable patients both decline rapidly over time, in adults as well as in children. This decline of short-term survival in relation to low-flow duration in ECPR was slower than in CCPR.

Trial registration: Prospero: CRD42020212480, 02-10-2020

Keywords: heart arrest, cardiac arrest, cardiopulmonary resuscitation, extracorporeal cardiopulmonary resuscitation, survival

INTRODUCTION

Despite mounting research, cardiac arrest remains a major cause of death worldwide. (1) Although improvements have been seen in the conventional cardiopulmonary resuscitation (CCPR), in the education of laypersons to perform basic life support (BLS), and in the use of defibrillators or automated external defibrillators, survival outcomes after cardiac arrest remain poor. Previous studies have shown that various prognostic factors are associated with short-term survival, including age, initial cardiac rhythm, time to return of spontaneous circulation (ROSC), whether or not bystanders attempt BLS, and how quickly this BLS is provided. (2-4) Of these prognostic factors, time to ROSC has a major influence on this short-term survival and – unlike factors such as age – is also a factor over which we have some control. (5)

One way of shortening the low-flow duration, could be the use of extracorporeal cardiopulmonary resuscitation (ECPR). ECPR involves applying an extracorporeal membrane oxygenator (ECMO) during CPR. The low-flow duration is defined as the elapsed interval from resuscitation until one of three endpoints: ROSC, artificial return of circulation using ECPR, or death. ECPR treatment is used to limit ischaemic damage and buy time to resolve the cause of cardiac arrest. In a randomised controlled trial survival outcome of ECPR patients was much higher than in CCPR patients. (6) Two recent meta-analyses, have shown the potential benefit on short-term survival of adding ECPR to CCPR. (7, 8) It is clear that the longer the low-flow state is present, the poorer the survival outcome will be. (9-11) The most recent meta-analysis showed that a shorter low-flow duration in ECPR is associated with improved survival. (8) Previously propensity matched observational studies show different results ranging from improved outcomes for ECPR, to no difference in outcomes for ECPR and CCPR. (12-17)

The aims of this systematic review and meta-analysis were therefore to determine (1) the relation of survival and low-flow duration of both ECPR and CCPR and (2) if ECPR and CCPR have different survival curves in relation to low-flow duration. We intended to stratify these analyses for adults and children and for out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA).

MATERIALS AND METHODS

This systematic review and meta-analysis is performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (18) and it is listed in the PROSPERO register with registration number CRD42020212480. Study eligibility criteria, search study selection, data extraction, and risk of bias assessment are described in detail in the Supplementary Material, Appendix 1. In short, a systematic

search in Embase, Medline, Web of Science, and Google Scholar was performed from inception up to April 2021. All studies including at least 20 OHCA or IHCA patients treated with ECPR or CCPR were included. Two researchers screened and included the studies and performed data extraction, including study characteristics, patient characteristics, clinical characteristics and outcomes.

Statistical analysis

The study characteristics, patient characteristics, clinical characteristics and outcomes were described for each study. The studies were grouped by adults, children, or both. We report continuous variables using mean and standard deviation (SD) or median and interquartile ranges (IQR) where applicable. We report categorical variables using numbers and percentages.

As primary outcome we studied the relation of short-term survival and low-flow duration. As secondary outcome the short-term survival in relation to low-flow duration of ECPR and CCPR were compared. Outcome measures differed by study. Studies in which hospital survival was mentioned, this was used as the primary outcome parameter. For studies in which only neurologically intact survival was mentioned, or 30-day, 90-day, or 1-year survival: all these outcome parameters were considered as 'hospital survival'. If only intensive care unit survival was mentioned in the study, these studies were excluded. In case no individual data was available, we contacted the authors for the exact low-flow durations, followed by a reminder after one month if necessary. If we received no response or if the data was not available, we used the time intervals of low-flow duration.

In order to be able to analyse the data of the studies which reported individual data, we had to cluster the low-flow durations with a minimum of five events per group. For the studies of which only low-flow duration intervals were available, we calculated the average value of every time interval per study, as this was the best possible approximation for the value of each individual patient. Next, for the maximum values, mostly a value 'higher than' (>) a specific value was mentioned. We approximated this value by calculating the mean (SD) and determined low-flow duration belonging to the 87.5 percentile. If there was no mean value mentioned in the articles, we used the median (IQR).

A linear mixed effect (LME) model was used to describe the course of survival over time in patients treated with ECPR and patients treated with CCPR, based on the study-specific and time-specific aggregated survival data. The LME model allows to account for clustering of data within a study and inverse variance weighing was applied. We ran separate analyses for several groups. We analysed data of adults and children separately. In adults and in children, we combined shockable and non-shockable initial cardiac rhythm for ECPR patients due to the limited amount of data. For CCPR patients shockable initial cardiac rhythm (CCPR-shockable) and non-shockable initial cardiac rhythm

(CCPR-non-shockable) were analysed separately. We compared ECPR patients to CCPR-shockable patients as shockable rhythm is usually an inclusion criterion for ECPR. Also, ECPR patients are mostly selected based on patient criteria which increase the chances of favourable outcome, as CCPR-shockable patients are the patients with expected better outcomes than in CCPR-non-shockable patients. In case studies including CCPR patients in which initial cardiac rhythm was not classified, were excluded for the analysis.

The short-term survival percentages we present are calculated using the following LME models. In adult ECPR patients (combining shockable and non-shockable initial cardiac rhythms): Hospital survival (%) = $2^{(5.5383-(0.02139*time))}$, time is being given in minutes of low-flow time. In adult CCPR-shockable patients: Hospital survival (%) = $2^{(7.5645-(0.1574*time))}$. Due to one highly influencing study, no LME model could be created for adult CCPR-non-shockable patients. In paediatric ECPR patients (combining shockable and non-shockable initial cardiac rhythms): Hospital survival (%) = $2^{(5.5139-(0.00442*time))}$. In paediatric CCPR-shockable patients: Hospital survival (%) = $2^{(6.8488-(0.08312*time))}$. In paediatric CCPR-non-shockable patients: Hospital survival (%) = $2^{(4.4677-(0.0598*time))}$. In order to compare the ECPR and CCPR-shockable patients we first arbitrarily determined a difference of 5% survival as clinically relevant. Next, we tested if there is any statistical difference between the course of the LME of ECPR and CCPR-shockable patients.

RESULTS

Study selection

We identified 5117 studies with our search, after removing duplicates there were 2461 studies remaining. After title and abstract screening, 193 studies were selected for full text screening. Of those, 48 were excluded because the outcomes were not presented in time intervals, 34 were excluded because the primary endpoint could not be obtained, nine were excluded because of multiple studies in the same cohort, nine studies were excluded because these only included patients achieving ROSC, and 51 were excluded for other reasons, as shown in Fig 1. Finally, we included 42 studies (N=417,133)(9, 11, 14, 19-57), of which 25 studies included only adult patients, 13 studies included only children, and four studies included both.

Characteristics

Table 1 shows the study characteristics and a more detailed description is shown in Table C of the Supplementary Material. Three of the adult studies included patients treated with ECPR or CCPR, 11 studies included only patients treated with ECPR, and 10 included only patients treated with CCPR. In the studies in children, one study included patients treated with ECPR or CCPR, five studies included only patients treated with ECPR, and

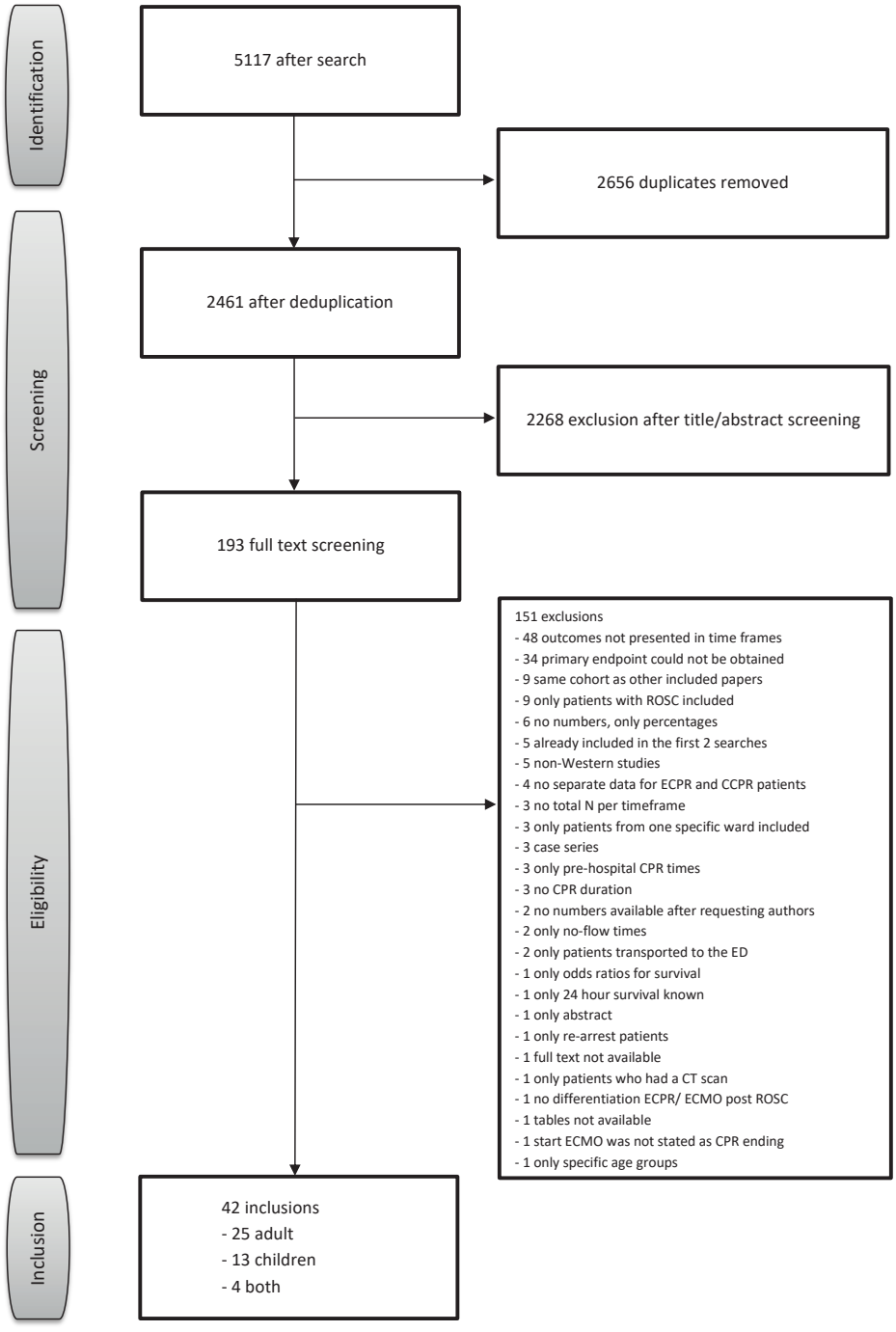


Figure 1 | Flowchart of study selection using the PRISMA guidelines

seven studies included only patients treated with CCPR. In the studies including both adults and children, one study included patients treated with ECPR or CCPR, two studies included only patients treated with ECPR, and one study included only patients treated with CCPR.

Patient and clinical characteristics are shown in Supplementary Material Table A. For the adult studies, 1470 patients treated with ECPR and 375,751 patients treated with CCPR were included. For the studies in children, 1140 patients treated with ECPR and 17,653 patients treated with CCPR were included. For the studies including both adults and children, 111 patients treated with ECPR and 436 patients treated with CCPR were included.

Table 1 | Study characteristics

No	Study	Year	Adults/ Children/ Both	Study design	Inclusion period	Setting (single/ multicenter)	Follow-up duration	ECPR/ CCPR/ both	Patient number
Studies in adults									
1	Adnet (8)	2017	Adults	descriptive	2011-2015	multi	30-days	CCPR	27301
2	Bartos (52)	2020	Adults	case-control	2015-2019	multi	hospital stay	both	1134
3	Chen (22)	2008	Adults	descriptive	1994-2005	single	5 years	ECPR	135
4	Chou (23)	2014	Adults	case-control	2006-2010	single	hospital stay	both	66
5	Dumot (24)	2001	Adults	descriptive	1994-1995	single	hospital stay	CCPR	445
6	Ferguson (25)	2008	Adults	descriptive	2001-2005	single	6 months	CCPR	256
7	Fjolner (26)	2017	Adults	descriptive	2011-2015	single	hospital stay	ECPR	21
8	Goldberger (26)	2012	Adults	descriptive	2000-2008	multi	hospital stay	CCPR	64339
9	Grunau (28)	2018	Adults	descriptive	2007-2011	multi	hospital stay	CCPR	5674
10	Haneya (48)	2012	Adults	descriptive	2007-2012	single	hospital stay	ECPR	85
11	Kim (13)	2014	Adults	cohort	2006-2013	single	3 months	both	499
12	Mandigers (56)	2021	Adults	descriptive	2010-2020	single	Hospital stay	ECPR	84
13	Murakami (53)	2020	Adults	descriptive	2010-2015	single	30-days	ECPR	1630
14	Nagao (35)	2016	Adults	descriptive	2005-2012	multi	30-days	CCPR	282183
15	Otani (36)	2018	Adults	descriptive	2009-2017	single	hospital stay	ECPR	135
16	Park (51)	2019	Adults	descriptive	2013-2016	multi	hospital stay	ECPR	689
17	Pionkowski (37)	1983	Adults	descriptive	1978-1982	single	hospital stay	CCPR	565
18	Pound (54)	2020	Adults	descriptive	2017-2018	multi	hospital stay	CCPR	152
19	Reynolds (39)	2016	Adults	descriptive	2007-2010	multi	hospital stay	CCPR	11368
20	Rosenberg (40)	1993	Adults	descriptive	1988-1989	multi	hospital stay	CCPR	300
21	Siao (58)	2020	Adults	descriptive	2012-2017	single	hospital stay	ECPR	112
22	Valentin (49)	1995	Adults	descriptive	1989-1991	single	hospital stay	CCPR	253
23	Wang (43)	2014	Adults	cohort	2007-2012	single	hospital stay	ECPR	230
24	Wengenmayer (10)	2017	Adults	cohort	2010-2016	single	hospital stay	ECPR	133

Table 1 | Study characteristics (*continued*)

No	Study	Year	Adults/ Children/ Both	Study design	Inclusion period	Setting (single/ multicenter)	Follow-up duration	ECPR/ CCPR/ both	Patient number
25	Yukawa (45)	2017	Adults	descriptive	2011-2015	single	hospital stay	ECPR	79
Studies in children									
26	Bembea (20)	2013	Children	descriptive	2000-2014	multi	hospital stay	ECPR	593
27	Ganesan (47)	2018	Children	descriptive	2012-2014	single	hospital stay	CCPR	137
28	Goto (27)	2016	Children	descriptive	2005-2012	multi	30-days	CCPR	12877
29	Innes (50)	1993	Children	descriptive	1990-1991	single	1 year	CCPR	41
30	Kalloghlian (30)	1998	Children	descriptive	1989-1992	single	hospital stay	CCPR	234
31	Kramer (55)	2020	Children	descriptive	2005-2016	single	hospital stay	ECPR	72
32	Lopez (32)	2004	Children	descriptive	1998-1999	multi	1 year	CCPR	283
33	Lopez (31)	2013	Children	descriptive	2007-2009	multi	hospital stay	CCPR	502
34	Matos (33)	2013	Children	descriptive	2000-2009	multi	hospital stay	both	3419
35	Meert (57)	2019	Children	descriptive	2009-2015	multi	1 year	ECPR	147
36	Morris (34)	2004	Children	cohort	1995-2002	single	hospital stay	ECPR	64
37	Rathore (38)	2016	Children	descriptive	2011-2012	single	1 year	CCPR	314
38	Sivarajan (42)	2011	Children	descriptive	1990-2006	single	2 year	ECPR	37
Studies in adults and children									
39	Chen (21)	2016	both	descriptive	2012	single	hospital stay	both	382
40	Hendrick (29)	1990	both	cohort	1986-1988	single	1-18 months	CCPR	90
41	Shinn (41)	2009	both	descriptive	2004-2006	single	hospital stay	ECPR	50
42	Younger (44)	1999	both	descriptive	1991-1998	single	hospital stay	ECPR	23

Study characteristics of the included papers. Extracorporeal cardiopulmonary resuscitation (ECPR), conventional cardiopulmonary resuscitation (CCPR).

Quality assessment

All available studies had an observational design: therefore, the overall quality of evidence was low. With respect to this low quality of evidence, we used the NOS to distinguish of quality within the included studies (Supplementary Material Table B).

Outcomes

The survival outcomes are shown in Table 2. In adults, short-term survival ranged from 9.3-46.4% in ECPR, and from 5.4-39.5% in CCPR. In children, short-term survival ranged from 34.4-40.6% in ECPR, and from 9.1-46.3% in CCPR. In the studies including both adults and children, short-term survival ranged from 19.4-36.0% in ECPR, and from 11.0-16.5% in CCPR.

Table 2 | Outcomes

No	Study	Short term survival (hospital/30 day)		Long term survival (3 months/6 months/ 1 year)		Survival with CPC score ≤2	
Studies in adults							
		ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
1	Adnet		1482 (5.4)				1249 (4.5)
2	Bartos	52 (39.0)	148 (23.0)	52 (39.0)		52 (39.0)	148 (23.0)
3	Chen	46 (34.1)		43 (31.9)		41 (30.4)	
4	Chou	15 (34.9)	5 (21.7)				
5	Dumot		104 (23.0)				
6	Ferguson		32 (13.0)		16 (6.0)		15 (5.9)
7	Fjolner	7 (33.3)				7 (33.3)	
8	Goldberger		9912 (15.4)				7034 (10.9%, 1188 missings)
9	Grunau		690 (12.2)				292 (5.1%, 306 missings)
10	Haneya	29 (34.1)				27 (31.7)	
11	Kim	9 (16.4)	86 (19.4)	8 (14.5)	44 (9.9)	8 (14.5)	36 (8.1)
12	Mandigers	24 (28.6)					
13	Murakami	32 (37.6)				14 (16.5)	
14	Nagao		21,658 (7.7)				9669 (3.4)
15	Otani	34 (25.0)				22 (16.3)	
16	Park	13 (9.3)				7 (5.0)	
17	Pionkowski	262 (46.4)					
18	Pound		60 (39.5)				43 (28.3)
19	Reynolds		1232 (10.8)				905 (8.0)
20	Rosenberg		82 (23.5)				
21	Siao	45 (40.2)		41 (36.6)		34 (30.4)	
22	Valentin		50 (19.8)				44 (17.4)
23	Wang	74 (32.2)				58 (25.2)	
24	Wengenmayer	19 (14.3)					
25	Yukawa	17 (21.5)				11 (13.9)	
Studies in children							
		ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
26	Bembea	241 (40.6)				108 (18.2%, 125 missings)	
27	Ganesan		27 (19.7)				21 (15.3)
28	Goto		1167 (9.1)				325 (2.5)
29	Innes		19 (46.3)		16 (39)		
30	Kalloghlian		66 (28.2)				

Table 2 | Outcomes (*continued*)

No	Study	Short term survival (hospital/30 day)		Long term survival (3 months/6 months/ 1 year)		Survival with CPC score ≤2	
31	Kramer	26 (36.1)		22 (30.6)		19 (26.4)	
32	Lopez		98 (34.6)		94 (33.2)		
33	Lopez		197 (39.2)				104 (88.9)
34	Matos	78 (34.4)	876 (27.4)				
35	Meert			32 (22.1)		39 (30.5)	
36	Morris	23 (35.9)	26 (35.6)			5 (50.0%, 3 missings)	
37	Rathore		44 (14.0)		35 (11.1)		27 (8.6)
38	Sivarajan	14 (37.8)		12 (32.4)		4 (10.8)	
Studies in adults and children							
		ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
35	Chen	7 (19.4)	38 (11.0)				
36	Hendrick		15 (16.5)				
37	Shinn	16 (32.0)					
38	Younger	9 (36.0)					

Survival outcome and neurologic favourable outcome for all included studies. Values are presented as number (%). Extracorporeal cardiopulmonary resuscitation (ECPR), conventional cardiopulmonary resuscitation (CCPR), cerebral performance category (CPC).

Primary and secondary outcome

In adults, both survival curves of ECPR patients and CCPR-shockable patients showed a decline in survival with increase of low-flow duration. When comparing the survival curves of adults, the decline in survival outcome for increasing low-flow duration was significantly slower ($p<0.01$) in patients treated with ECPR than in CCPR-shockable patients, as shown in Fig. 2. Short-term survival at 15 minutes low-flow duration was 37.2% in ECPR and 36.8% in CCPR-shockable. In ECPR, short term survival declined, from 34.5% at 20 minutes, to 29.8% at 30 minutes, 23.8% at 45 minutes, and 19.1% at 60 minutes. In CCPR-shockable, short-term survival declined, from 21.4% at 20 minutes to 7.2% at 30 minutes, 1.4% at 45 minutes, and 0.3% at 60 minutes. The difference in survival outcome was at least 5% higher in ECPR than in CCPR-shockable starting from 16.5 minutes. This difference increased to 22.6% at 30 minutes and 18.8% at 60 minutes low-flow duration. Unfortunately, we were unable to estimate a linear mixed model for CCPR-non-shockable patients due to major influence of one study.

In children, all of the survival curves of ECPR patients, CCPR-shockable patients, and CCPR-non-shockable patients showed a decline in survival with increase of low-

flow duration. When comparing the survival curves of children, the decline in survival outcomes for increasing low-flow duration was significantly slower ($p<0.01$) in patients treated with ECPR than in CCPR-shockable patients, as shown in Fig. 3. In ECPR, short-term survival declined from 43.6% at 15 minutes to 41.7% at 30 minutes, 39.8% at 45 minutes, and 38.0% at 60 minutes. In CCPR-shockable patients, short-term survival declined from 48.6% at 15 minutes to 20.5% at 30 minutes, 8.6% at 45 minutes, and 3.6% at 60 minutes. In CCPR-non-shockable patients, short-term survival declined from 11.9% at 15 minutes to 6.4% at 30 minutes, 3.4% at 45 minutes, and 1.8% at 60 minutes. The short-term survival was at least 5% higher in ECPR than in CCPR-shockable patients starting from 19.2 minutes. This difference increased to 21.2% at 30 minutes, and 34.4% at 60 minutes low-flow duration.

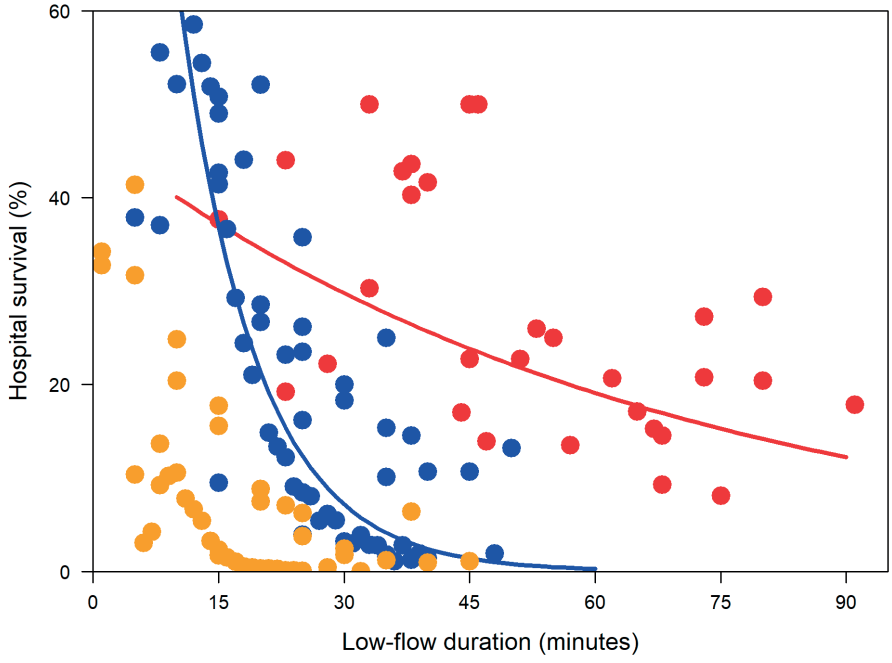


Figure 2 | Relation between low-flow duration in minutes and hospital survival in percentage in adult patients treated with extracorporeal cardiopulmonary resuscitation (ECPR, red: Hospital survival (%) = $2^{(5.5383-(0.02139*\text{time (in minutes)}))}$), conventional cardiopulmonary resuscitation (CCPR) due to shockable initial cardiac rhythms (blue: Hospital survival (%) = $2^{(7.5645-(0.1574*\text{time (in minutes)}))}$), CCPR due to non-shockable initial cardiac rhythms (yellow). Calculated using LME models shown above. Due to one highly influencing study, no LME model could be created for CCPR patients with non-shockable cardiac rhythm.

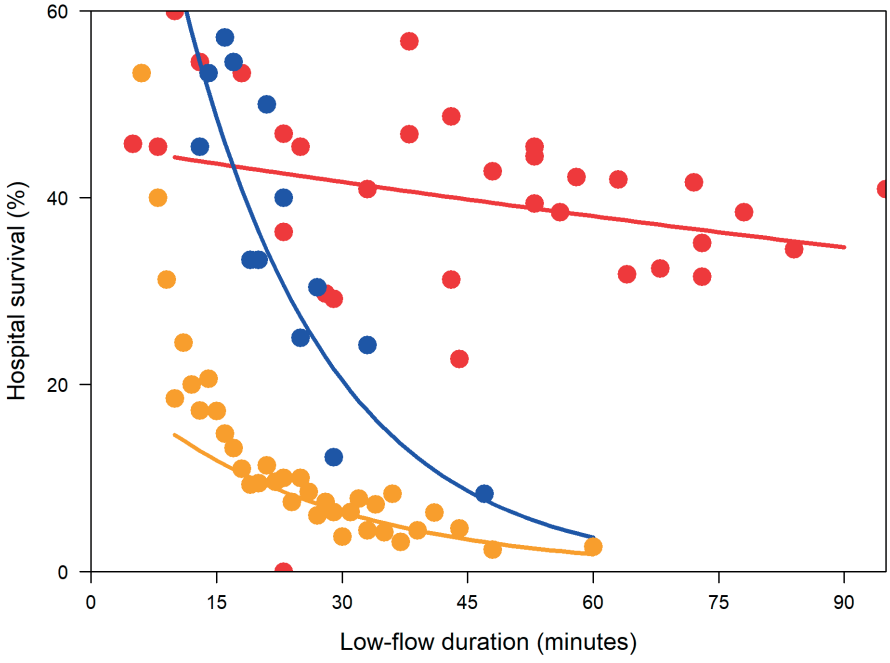


Figure 3 | Relation between low-flow duration in minutes and hospital term survival in percentage in children treated with extracorporeal cardiopulmonary resuscitation (ECPR, red: Hospital survival (%) = $2^{(5.5139-(0.00442*\text{time (minutes)}))}$), conventional cardiopulmonary resuscitation (CCPR) due to shockable initial cardiac rhythms (blue: Hospital survival (%) = $2^{(6.8488-(0.08312*\text{ time (minutes)}))}$), CCPR due to non-shockable initial cardiac rhythms (yellow: Hospital survival (%) = $2^{(4.4677-(0.0598*\text{ time (minutes)}))}$). Calculated using LME models shown above.

DISCUSSION

The results of our systematic review and meta-analysis shows a decline in survival with increase of low-flow duration in both ECPR and CCPR patients. This decline in short-term survival for increasing low-flow duration is significantly slower in patients treated with ECPR than in CCPR-shockable patients, for both adults as children.

The fact that we found a slower decline in survival for increasing low-flow duration in favour of ECPR in both adults and children is in line with the findings of a previous study by Bartos et al. (51) They recently compared survival outcomes of adults treated with ECPR and CCPR for increasing low-flow durations and found the decline in neurologically favourable survival to be slower in ECPR than in CCPR. (51) Although this study was performed in a smaller group of patients and used a slightly different outcome (neurologically favourable survival rather than just survival), the slower decline in survival for ECPR was similar to that seen in our results. This difference in the decline of short-term

survival implies that the sooner ECPR is performed, the greater the chances of a favourable outcome.

The finding in our study that survival outcomes in ECPR are higher than those of CCPR is generally in line with the results of previous studies. (7, 8) In the first randomised controlled trial comparing ECPR to CCPR, Yannopoulos et al (6) found a short-term survival rate of 43% in ECPR patients and 7% in CCPR patients. Previous systematic reviews comparing patients treated with ECPR and patients treated with CCPR have also shown higher survival outcomes (7, 8) and better neurological outcomes (8) in favour of ECPR. While two other recent systematic reviews did not observe this beneficial result for ECPR in OHCA patients, they did observe such a benefit in IHCA patients. (58, 59) Unfortunately, due to a lack of data, we were not able to analyse the outcomes for OHCA and IHCA separately. However, as indicated by Holmberg et al (59), OHCA patients most likely experience longer low-flow durations than IHCA patients. The outcome difference of OHCA and IHCA is most probably caused by the difference in low-flow duration, the cause of the arrest, and the primary rhythm.

With this study, we emphasize the importance of limiting the low-flow duration in both ECPR and CCPR patients. However, in most of the ECPR cases, low-flow durations shorter than 30 minutes are not always feasible. Especially in OHCA patients, the time until arrival to the hospital varies worldwide between 30-60 minutes. (60-62) Based on our results we would suggest start preparing for ECPR – retrieve vascular access without dilatation – could be started before cannulation. Definitive cannulation could be started at 20 minutes low-flow duration. Worldwide, there are limited centers providing ECPR in the field (62), all others can only start ECPR after hospital arrival. Therefore, exploring the means for rapid transportation to the hospital or the ability to perform ECPR in the field are important in an attempt to decrease the low-flow duration. Several studies are recruiting patients or extending their study to research ECPR in the pre-hospital setting. (6, 63, 64)

Limitations

This study has some limitations. First, all studies that we included are influenced by confounding by indication. There is still no worldwide consensus regarding which patients are eligible for ECPR. Secondly, because of the lack of individual patient data we were not able to analyse OHCA and IHCA patients separately. When we stratified the data for ECPR and CCPR in time intervals and tried to stratify for OHCA and IHCA, the amount of data per cell was too limited to analyse. Due to the different causes of cardiac arrest in these two groups and the expected difference in the delay before starting CPR, this factor will probably influence the prognosis. Thirdly, by combining survival outcomes with favourable neurological outcomes in cases where raw survival outcomes were not given, some of the used data will be an underestimation of the survival outcomes. We included

these outcomes as short-term survival in order to avoid overestimating. Fourthly, all of the available studies are observational studies which hampers strong recommendations based on this study. Finally, since we could not include all of the individual patient data, we had to determine average low-flow durations in order to pool the survival data. To overcome such a limitation in future meta-analysis – for example including the randomized controlled trials comparing ECPR and CCPR that are currently being conducted – these data should be pooled based on individual low-flow durations. This will allow for a more accurate comparison between the two groups.

CONCLUSION

The short-term survival of ECPR and CCPR-shockable patients both decline rapidly over time, in adults as well as in children. This decline of short-term survival in relation to low-flow duration in ECPR was lower than in CCPR.

REFERENCES

1. Organisation WH. https://www.who.int/ 2020 [Available from: https://www.who.int/.
2. Fernando SM, Tran A, Cheng W, Rochwerg B, Taljaard M, Vaillancourt C, et al. Pre-arrest and intra-arrest prognostic factors associated with survival after in-hospital cardiac arrest: systematic review and meta-analysis. BMJ. 2019;367:l6373.
3. Patz T, Stelzig K, Pfeifer R, Pittl U, Thiele H, Busch HJ, et al. Age-associated outcomes after survived out-of-hospital cardiac arrest and subsequent target temperature management. Acta Anaesthesiol Scand. 2019;63(8):1079-88.
4. Zhang Q, Qi Z, Liu B, Li C. Predictors of survival and favorable neurological outcome in patients treated with targeted temperature management after cardiac arrest: A systematic review and meta-analysis. Heart Lung. 2018;47(6):602-9.
5. Lee SH, Jung JS, Lee KH, Kim HJ, Son HS, Sun K. Comparison of Extracorporeal Cardiopulmonary Resuscitation with Conventional Cardiopulmonary Resuscitation: Is Extracorporeal Cardiopulmonary Resuscitation Beneficial? Korean J Thorac Cardiovasc Surg. 2015;48(5):318-27.
6. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. Lancet. 2020;396(10265):1807-16.
7. Ouweneel DM, Schotborgh JV, Limpens J, Sjauw KD, Engstrom AE, Lagrand WK, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. Intensive Care Med. 2016;42(12):1922-34.
8. Twohig CJ, Singer B, Grier G, Finney SJ. A systematic literature review and meta-analysis of the effectiveness of extracorporeal-CPR versus conventional-CPR for adult patients in cardiac arrest. J Intensive Care Soc. 2019;20(4):347-57.
9. Adnet F, Triba MN, Borron SW, Lapostolle F, Hubert H, Gueugniaud PY, et al. Cardiopulmonary resuscitation duration and survival in out-of-hospital cardiac arrest patients. Resuscitation. 2017;111:74-81.
10. Martinell L, Nielsen N, Herlitz J, Karlsson T, Horn J, Wise MP, et al. Early predictors of poor outcome after out-of-hospital cardiac arrest. Crit Care. 2017;21(1):96.
11. Wengenmayer T, Rombach S, Ramshorn F, Biever P, Bode C, Duerschmied D, et al. Influence of low-flow time on survival after extracorporeal cardiopulmonary resuscitation (eCPR). Crit Care. 2017;21(1):157.
12. Blumenstein J, Leick J, Liebetrau C, Kempfert J, Gaede L, Gross S, et al. Extracorporeal life support in cardiovascular patients with observed refractory in-hospital cardiac arrest is associated with favourable short and long-term outcomes: A propensity-matched analysis. Eur Heart J Acute Cardiovasc Care. 2016;5(7):13-22.
13. Choi DS, Kim T, Ro YS, Ahn KO, Lee EJ, Hwang SS, et al. Extracorporeal life support and survival after out-of-hospital cardiac arrest in a nationwide registry: A propensity score-matched analysis. Resuscitation. 2016;99:26-32.
14. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. Crit Care. 2014;18(5):535.
15. Lasa JJ, Rogers RS, Localio R, Shults J, Raymond T, Gaies M, et al. Extracorporeal Cardiopulmonary Resuscitation (E-CPR) During Pediatric In-Hospital Cardiopulmonary Arrest Is Associated With

Improved Survival to Discharge: A Report from the American Heart Association's Get With The Guidelines-Resuscitation (GWTG-R) Registry. Circulation. 2016;133(2):165-76.
16. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. Crit Care Med. 2013;41(5):1186-96.
17. Patricio D, Peluso L, Brasseur A, Lheureux O, Belliato M, Vincent JL, et al. Comparison of extracorporeal and conventional cardiopulmonary resuscitation: a retrospective propensity score matched study. Crit Care. 2019;23(1):27.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
19. Bembea MM, Ng DK, Rizkalla N, Rycus P, Lasa JJ, Dalton H, et al. Outcomes After Extracorporeal Cardiopulmonary Resuscitation of Pediatric In-Hospital Cardiac Arrest: A Report From the Get With the Guidelines-Resuscitation and the Extracorporeal Life Support Organization Registries. Crit Care Med. 2019;47(4):e278-e85.
20. Chen CT, Chiu PC, Tang CY, Lin YY, Lee YT, How CK, et al. Prognostic factors for survival outcome after in-hospital cardiac arrest: An observational study of the oriental population in Taiwan. J Chin Med Assoc. 2016;79(1):11-6.
21. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet. 2008;372(9638):554-61.
22. Chou TH, Fang CC, Yen ZS, Lee CC, Chen YS, Ko WJ, et al. An observational study of extracorporeal CPR for in-hospital cardiac arrest secondary to myocardial infarction. Emerg Med J. 2014;31(6):441-7.
23. Dumot JA, Burval DJ, Sprung J, Waters JH, Mraovic B, Karafa MT, et al. Outcome of adult cardiopulmonary resuscitations at a tertiary referral center including results of "limited" resuscitations. Arch Intern Med. 2001;161(14):1751-8.
24. Ferguson RP, Phelan T, Haddad T, Hinduja A, Dubin NH. Survival after in-hospital cardiopulmonary resuscitation. South Med J. 2008;101(10):1007-11.
25. Goldberger ZD, Chan PS, Berg RA, Kronick SL, Cooke CR, Lu M, et al. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. Lancet. 2012;380(9852):1473-81.
26. Goto Y, Funada A, Goto Y. Duration of Prehospital Cardiopulmonary Resuscitation and Favorable Neurological Outcomes for Pediatric Out-of-Hospital Cardiac Arrests: A Nationwide, Population-Based Cohort Study. Circulation. 2016;134(25):2046-59.
27. Grunau B, Puyat J, Wong H, Scheuermeyer FX, Reynolds JC, Kawano T, et al. Gains of Continuing Resuscitation in Refractory Out-of-hospital Cardiac Arrest: A Model-based Analysis to Identify Deaths Due to Intra-arrest Prognostication. Prehosp Emerg Care. 2018;22(2):198-207.
28. Hendrick JM, Pijls NH, van der Werf T, Crul JF. Cardiopulmonary resuscitation on the general ward: no category of patients should be excluded in advance. Resuscitation. 1990;20(2):163-71.
29. Kalloghlian AK, Matthews NT, Khan BA. Outcome of in-hospital pediatric cardiac arrest. Ann Saudi Med. 1998;18(3):208-11.
30. Lopez-Herce J, Del Castillo J, Matamoros M, Canadas S, Rodriguez-Calvo A, Cecchetti C, et al. Factors associated with mortality in pediatric in-hospital cardiac arrest: a prospective multicenter multinational observational study. Intensive Care Med. 2013;39(2):309-18.

31. Lopez-Herce J, Garcia C, Dominguez P, Carrillo A, Rodriguez-Nunez A, Calvo C, et al. Characteristics and outcome of cardiorespiratory arrest in children. Resuscitation. 2004;63(3):311-20.
32. Matos RI, Watson RS, Nadkarni VM, Huang HH, Berg RA, Meaney PA, et al. Duration of cardiopulmonary resuscitation and illness category impact survival and neurologic outcomes for in-hospital pediatric cardiac arrests. Circulation. 2013;127(4):442-51.
33. Morris MC, Wernovsky G, Nadkarni VM. Survival outcomes after extracorporeal cardiopulmonary resuscitation instituted during active chest compressions following refractory in-hospital pediatric cardiac arrest. Pediatr Crit Care Med. 2004;5(5):440-6.
34. Nagao K, Nonogi H, Yonemoto N, Gaieski DF, Ito N, Takayama M, et al. Duration of Prehospital Resuscitation Efforts After Out-of-Hospital Cardiac Arrest. Circulation. 2016;133(14):1386-96.
35. Otani T, Sawano H, Natsukawa T, Nakashima T, Oku H, Gon C, et al. Low-flow time is associated with a favorable neurological outcome in out-of-hospital cardiac arrest patients resuscitated with extracorporeal cardiopulmonary resuscitation. J Crit Care. 2018;48:15-20.
36. Pionkowski RS, Thompson BM, Gruchow HW, Aprahamian C, Darin JC. Resuscitation time in ventricular fibrillation--a prognostic indicator. Ann Emerg Med. 1983;12(12):733-8.
37. Rathore V, Bansal A, Singhi SC, Singhi P, Muralidharan J. Survival and neurological outcome following in-hospital paediatric cardiopulmonary resuscitation in North India. Paediatr Int Child Health. 2016;36(2):141-7.
38. Reynolds JC, Grunau BE, Rittenberger JC, Sawyer KN, Kurz MC, Callaway CW. Association between Duration of Resuscitation and Favorable Outcome after Out-of-Hospital Cardiac Arrest: Implications for Prolonging or Terminating Resuscitation. Circulation. 2016;134(25):2084-94.
39. Rosenberg M, Wang C, Hoffman-Wilde S, Hickam D, Hickham DctHD. Results of cardiopulmonary resuscitation. Failure to predict survival in two community hospitals. Arch Intern Med. 1993;153(11):1370-5.
40. Shinn SH, Lee YT, Sung K, Min S, Kim WS, Park PW, et al. Efficacy of emergent percutaneous cardiopulmonary support in cardiac or respiratory failure: fight or flight? Interact Cardiovasc Thorac Surg. 2009;9(2):269-73.
41. Sivarajan VB, Best D, Brizard CP, Shekerdemian LS, d'Udekem Y, Butt W. Duration of resuscitation prior to rescue extracorporeal membrane oxygenation impacts outcome in children with heart disease. Intensive Care Med. 2011;37(5):853-60.
42. Wang CH, Chou NK, Becker LB, Lin JW, Yu HY, Chi NH, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest--a comparison with that for extracorporeal rescue for in-hospital cardiac arrest. Resuscitation. 2014;85(9):1219-24.
43. Younger JG, Schreiner RJ, Swaniker F, Hirschl RB, Chapman RA, Bartlett RH. Extracorporeal resuscitation of cardiac arrest. Acad Emerg Med. 1999;6(7):700-7.
44. Yukawa T, Kashiura M, Sugiyama K, Tanabe T, Hamabe Y. Neurological outcomes and duration from cardiac arrest to the initiation of extracorporeal membrane oxygenation in patients with out-of-hospital cardiac arrest: a retrospective study. Scand J Trauma Resusc Emerg Med. 2017;25(1):95.
45. Fjølner J, Greisen J, Jørgensen MRS, Terkelsen CJ, Ilkjær LB, Hansen TM, et al. Extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest in a Danish health region. Acta Anaesthesiol Scand. 2017;61(2):176-85.
46. Ganesan RG, Das S, Parameswara N, Biswal N, Pabhu A. Survival after in-hospital cardiac arrest among paediatric patients-A descriptive study. J Clin Diagn Res. 2018;12(2):SC04-SC9.
47. Haneya A, Philipp A, Diez C, Schopka S, Bein T, Zimmermann M, et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. Resuscitation. 2012;83(11):1331-7.

48. Valentin A, Karnik R, Donath P, Winkler WB, Slany J. Outcome of cardiopulmonary resuscitation in hospitalized patients. RESUSCITATION. 1995;30(3):217-21.
49. Innes PA, Summers CA, Boyd IM, Molyneux EM. Audit of Pediatric Cardiopulmonary-Resuscitation. Archives of Disease in Childhood. 1993;68(4):487-91.
50. Park JH, Song KJ, Shin SD, Ro YS, Hong KJ. Time from arrest to extracorporeal cardiopulmonary resuscitation and survival after out-of-hospital cardiac arrest. Emerg Med Australas. 2019;31(6):1073-81.
51. Bartos JA, Grunau B, Carlson C, Duval S, Ripeckyj A, Kalra R, et al. Improved Survival with Extracorporeal Cardiopulmonary Resuscitation Despite Progressive Metabolic Derangement Associated with Prolonged Resuscitation. Circulation. 2020.
52. Murakami N, Kokubu N, Nagano N, Nishida J, Nishikawa R, Nakata J, et al. Prognostic Impact of No-Flow Time on 30-Day Neurological Outcomes in Patients With Out-of-Hospital Cardiac Arrest Who Received Extracorporeal Cardiopulmonary Resuscitation. Circ J. 2020;84(7):1097-104.
53. Pound G, Jones D, Eastwood GM, Paul E, Hodgson CL, Investigators A-C. Survival and functional outcome at hospital discharge following in-hospital cardiac arrest (IHCA): A prospective multicentre observational study. Resuscitation. 2020;155:48-54.
54. Kramer P, Mommsen A, Miera O, Photiadis J, Berger F, Schmitt KRL. Survival and Mid-Term Neurologic Outcome After Extracorporeal Cardiopulmonary Resuscitation in Children. Pediatr Crit Care Med. 2020;21(6):e316-e24.
55. Mandigers L, den Uil CA, Bunge JJH, Gommers D, Dos Reis Miranda D. Initial Arterial pCO2 and Its Course in the First Hours of Extracorporeal Cardiopulmonary Resuscitation Show No Association with Recovery of Consciousness in Humans: A Single-Centre Retrospective Study. Membranes (Basel). 2021;11(3).
56. Meert KL, Guerguerian AM, Barbaro R, Slomine BS, Christensen JR, Berger J, et al. Extracorporeal Cardiopulmonary Resuscitation: One-Year Survival and Neurobehavioral Outcome Among Infants and Children With In-Hospital Cardiac Arrest. Crit Care Med. 2019;47(3):393-402.
57. Siao FY, Chiu CW, Chiu CC, Chang YJ, Chen YC, Chen YL, et al. Can we predict patient outcome before extracorporeal membrane oxygenation for refractory cardiac arrest? Scand J Trauma Resusc Emerg Med. 2020;28(1):58.
58. Chen Z, Liu C, Huang J, Zeng P, Lin J, Zhu R, et al. Clinical Efficacy of Extracorporeal Cardiopulmonary Resuscitation for Adults with Cardiac Arrest: Meta-Analysis with Trial Sequential Analysis. Biomed Res Int. 2019;2019:6414673.
59. Holmberg MJ, Geri G, Wiberg S, Guerguerian AM, Donnino MW, Nolan JP, et al. Extracorporeal cardiopulmonary resuscitation for cardiac arrest: A systematic review. Resuscitation. 2018;131:91-100.
60. Funada A, Goto Y, Tada H, Teramoto R, Shimojima M, Hayashi K, et al. Duration of cardiopulmonary resuscitation in patients without prehospital return of spontaneous circulation after out-of-hospital cardiac arrest: Results from a severity stratification analysis. Resuscitation. 2018;124:69-75.
61. Gregers E, Kjaergaard J, Lippert F, Thomsen JH, Kober L, Wanscher M, et al. Refractory out-of-hospital cardiac arrest with ongoing cardiopulmonary resuscitation at hospital arrival - survival and neurological outcome without extracorporeal cardiopulmonary resuscitation. Crit Care. 2018;22(1):242.
62. Lamhaut L, Hutin A, Puymirat E, Jouan J, Raphalen JH, Jouffroy R, et al. A Pre-Hospital Extracorporeal Cardio Pulmonary Resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: An observational study and propensity analysis. Resuscitation. 2017;117:109-17.

63. Singer B, Reynolds JC, Davies GE, Wrigley F, Whitbread M, Faulkner M, et al. Sub30: Protocol for the Sub30 feasibility study of a pre-hospital Extracorporeal membrane oxygenation (ECMO) capable advanced resuscitation team at achieving blood flow within 30 min in patients with refractory out-of-hospital cardiac arrest. Resusc Plus. 2020;4:100029.
64. Miranda DdR. ON-SCENE Initiation of Extracorporeal CardioPulmonary Resuscitation During Refractory Out-of-Hospital Cardiac Arrest (ON-SCENE): Clinicaltrials.gov; 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT04620070.

SUPPLEMENTARY MATERIAL

Appendix 1: Detailed description of material and methods

Study eligibility

We included research performed in adults, children, or both, suffering from an out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA) and treated with ECPR or CCPR. Any type of study was included that contained at least 20 patients. In order to get the closest approach of individual data, we only included studies with survival outcomes mentioned for categorised low-flow durations in at least three time groups or studies with individual patient data. All authors of eligible studies with only mean or median low-flow durations for survivors and non-survivors were contacted for individual data. In case this data could not be provided, these studies were excluded.

Search

A systematic search of the following databases was conducted by a medical information specialist: Embase, Medline, Web of Science, and Google Scholar. This was done from inception up to April 2021. Search terms which were used were, among others: 'time factor', 'cardiopulmonary resuscitation', 'duration', 'survival', and their synonyms (shown in Supplementary Material, Appendix 2). Non-human studies, studies in new-borns, non-English studies, and conference abstracts were excluded by negation and/or excluding words in the title.

Study selection

Two independent researchers (L.M. and D.R.M.) screened all articles for relevance on title and abstract. After selecting the articles for full text screening, they discussed the disagreements. Next, these two researchers screened the selected full text papers regarding the inclusion and exclusion criteria. If there were any disagreements about selecting full text papers for this review, these were also discussed.

Data Extraction

The data extraction was performed by the same two researchers. Data extraction included: study characteristics (author, year, adults/children/both, study design, inclusion period, single centre or multicentre setting, follow-up duration, ECPR/CCPR/both, the overall included patient number, and the primary aim), patient and clinical characteristics (age, sex, OHCA/IHCA, initial cardiac rhythm, witnessed arrest, bystander CPR, ROSC, and low-flow duration), and outcomes (short-term survival [hospital or 30-day survival], long-term survival [3 months, 6 months, or 1 year survival], and survival with favourable

neurological outcome [stated as cerebral performance category (CPC) score ≤2]). The classification of the type of study design was based on the study of Grimes et al. (19)

Risk of bias assessment

The risk of bias and quality was high due to the heterogeneity of the included studies. In order to attempt to assess this risk of bias, we used the Newcastle-Ottawa Scale (NOS) (20), because all available studies were observational. The assessment was performed by one researcher (L.M.). In case something was unclear, this was discussed with the senior researcher (D.R.M.).

Appendix 2: Systematic search dd 08-04-2021

embase.com

((('treatment duration'/de OR 'time factor'/de) AND ('resuscitation'/exp)) OR (((duration OR length OR prolong* OR long* OR short* OR minutes) NEAR/6 (resuscitat* OR reanimat* OR cpr OR ecpr)) OR (((duration OR length) NEAR/6 (ischem*) OR low-flow-time) AND (resuscitat* OR reanimat* OR cpr OR ecpr))):ab,ti,kw) AND ('survival'/exp OR 'mortality'/exp OR 'death'/de OR 'fatality'/de OR ((favorab* NEAR/3 neurol* NEAR/3 outcome*) OR surviv* OR mortalit* OR death OR die OR died OR fatal*):ab,ti,kw) NOT ('case report'/de OR ('case report*'):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim NOT ([Conference Abstract]/lim) NOT ('newborn'/exp OR (newborn* OR neonat* OR apgar):ab,ti,kw)

Medline Ovid

(((*Time Factors/) AND (Resuscitation/ OR exp Cardiopulmonary Resuscitation/)) OR (((duration OR length OR prolong* OR long* OR short* OR minutes) ADJ6 (resuscitat* OR reanimat* OR cpr OR ecpr)) OR (((duration OR length) ADJ6 (ischem*) OR low-flow-time) AND (resuscitat* OR reanimat* OR cpr OR ecpr))).ab,ti,kf.) AND (exp Survival/ OR exp Mortality/ OR Death/ OR ((favorab* ADJ3 neurol* ADJ3 outcome*) OR surviv* OR mortalit* OR death OR die OR died OR fatal*).ab,ti,kf.) NOT (case reports/ OR (case report*).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la. NOT (Infant, Newborn/ OR (newborn* OR neonat* OR apgar).ab,ti,kf.)

Web of science

TS=(((((“duration” OR “length” OR prolong* OR long* OR short* OR “minutes”) NEAR/5 (resuscitat* OR reanimat* OR “cpr” OR “ecpr”)) OR ((((“duration” OR “length”) NEAR/5 (ischem*) OR “low-flow-time”) AND (resuscitat* OR reanimat* OR “cpr” OR “ecpr”)))) AND (((favorab* NEAR/2 neurol* NEAR/2 outcome*) OR surviv* OR mortalit* OR “death” OR “die” OR “died” OR fatal*)) NOT ((“case report*”)) NOT ((animal* OR rat OR rats OR mouse

OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man))) AND DT=(Article OR Review OR Letter OR Early Access) AND LA=(english)

Google scholar

"prolonged|long|short resuscitation|reanimation|cpr|ecpr"|"duration|length*resuscitation|reanimation|cpr|ecpr"|"resuscitation|reanimation|cpr|ecpr duration|length"|"low-flow-time""favorable neurologic outcomes"|survival|mortality|fatality -"case report"

'prolonged|long|short resuscitation|reanimation|cpr|ecpr'|'duration|length*resuscitation|reanimation|cpr|ecpr'|'resuscitation|reanimation|cpr|ecpr duration|length'|'low-flow-time''favorable neurologic outcomes'|survival|mortality|fatality -'case report'

Total number after deduplication: 2461

Appendix 3: Formulas

Adults

1. ECPR, shockable/non-shockable: Hospital survival (%) = $2^{(5.5383-(0.02139*\text{time (in minutes)}))}$
2. CCPR, shockable: Hospital survival (%) = $2^{(7.5645-(0.1574*\text{time (in minutes)}))}$

Children

1. ECPR, shockable/non-shockable: Hospital survival (%) = $2^{(5.5139-(0.00442*\text{time (minutes)}))}$
2. CCPR, shockable: Hospital survival (%) = $2^{(6.8488-(0.08312*\text{ time (minutes)}))}$
3. CCPR, non-shockable: Hospital survival (%) = $2^{(4.4677-(0.0598*\text{ time (minutes)}))}$

Table A (1) | Patient characteristics and clinical characteristics

Number	Study	Included patient number (n=)		Age (years)		Male (%)	
		ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
Studies in adults							
1	Adnet		9095		71 (10-90th%: 58-82)		17,728 (64.9)
2	Bartos	133	654	57 (1.0)	59 (0.4)	126 (79.0)	528 (81.0)
3	Chen	135		56 (16-87)		90 (66.7)	
4	Chou	43	23	60.5 (11.6)	69.6 (13.3)	43 (93.0)	17 (73.9)
5	Dumot		445		NR		251 (56.4)
6	Ferguson		256		64 (range:19-96)		139 (54.3)
7	Fjolner	21		56 (19-73)		12 (57.0)	
8	Goldberger		64,339		NR		37,141 (57.7)
9	Grunau		5674		68 (55-80)		3782 (67.0)
10	Haneya	85		59 (16), 57(47-73)		61 (71.8)	
11	Kim	55	444	53 (41-68)	69 (56-77)	285 (64.1)	41 (74.5)
12	Mandigers	84		46.9 (15.6)		53 (63.1)	
13	Murakami	85		56.7 (11.6)		70 (82.4)	
14	Nagao		282,183		NR		171,202 (60.7)
15	Otani	135		65 (50-72)		115 (85.0)	
16	Park	140		56 (46-63.5)		116 (82.9)	
17	Pionkowski		565		mean 65		435 (77.0)
18	Pound		152		70.2 (13.9)		101 (66.4)
19	Reynolds		11,368		NR		7121 (62.6)
20	Rosenberg		300		70,4		165 (55.0)
21	Valentin		253		69.5 (13.3)		145 (57.3)
22	Siao	112		59.5 (50.0-67.5)		83 (74.1)	
23	Wang	230		NR		178 (77.4)	
24	Wengenmayer	133		58.7 (2.6)		99 (74.4)	
25	Yukawa	79		59 (48.5-64.5)		65 (82.3)	
Total		**1470**	**375,751**				
Studies in children							
26	Bembea	593		2.9m (11d-20m)		351 (59.1)	
27	Ganesan		137		NR		80 (58.4)
28	Goto		12,877		1 (0-12)		7852 (61.0)
29	Innes		41		NR		23 (56.1)
30	Kalloghlian		234		mean 16.8m, median 9m		NR
31	Kramer	72		0.34 (0.04-1.89)			38 (52.8)

Table A (1) | Patient characteristics and clinical characteristics (*continued*)

Number	Study	Included patient number (n=)		Age (years)		Male (%)	
32	Lopez		283		48m (54.4m)		185 (65.4)
33	Lopez		502		44.7m (58.5m)		276 (55.0)
34	Matos	227	3192	NR	NR	NR	NR
35	Meert	147		NR		94 (63.9)	
36	Morris	64	73	NR		NR	NR
37	Rathore		314		2 (6m-5y+1m)		204 (65.0)
38	Sivarajan	37		22d (8d-150d)		19 (51.4)	
Total		**1140**	**17,653**				

Number	Study	Included patient number (n=)		Age (years)		Male (%)	
		ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
Studies in adults and children							
39	Chen	36	346	NR	NR	NR	NR
40	Hendrick		90		48.9 (range 2 months – 89 years)		49 (54.4)
41	Shinn	50		NR		NR	
42	Younger	25		35.7 (15.3)			
Total		**111**	**436**				

Table A (2) | Patient characteristics and clinical characteristics

Number	OHCA (%)		Initial shockable rhythm (%)		Witnessed (%)		Bystander CPR (%)	
	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
Studies in adults								
1		27,301 (100.0)		3814 (14.0)		NR		11,900 (43.6)
2	160 (100.0)	654 (100.0)	160 (100.0)	654 (100.0)	121 (76.0)	454 (69.0)	105 (66.0)	376 (57.0)
3	0 (0.0)		97 (71.9)		133 (98.5)		NR	
4	0 (0.0)	0 (0.0)	26 (60.5)	9 (39.1)	NR	NR	NR	NR
5		NR		NR		389 (87.4)		NR
6		0 (0.0)		41 (16.0)		NR		NR
7	21 (100.0)		9 (42.9)		21 (100.0)		21 (100.0)	
8		0 (0.0)		12,924 (20.1)		49,918 (77.6)		NR
9		5674 (100.0)		1461 (26.0)		2789 (49.2)		2397 (42.0)
10	26 (30.6)		25 (29.4)		NR		NR	
11	55 (100.0)	444 (100.0)	31 (56.4)	85 (19.1)	43 (78.2)	328 (73.9)	23 (41.8)	151 (34.0)
12	38 (45.2)		26 (31.0)		78 (92.9)		37 (44)	
13	85 (100.0)		70 (82.4)		70 (82.4)		43 (50.6)	
14		282,183 (100.0)		42,411 (15.0)		282,183 (100.0)		127,240 (45.1)
15	135 (100.0)		87 (64.0)		135 (100.0)		74 (55.0)	
16	140 (100.0)		79 (56.4)		140 (100.0)		105 (75.0)	
17		NR		565 (100.0)		256 (45.3)		82 (14.5)
18		0 (0.0)		34 (22.3)		116 (76.3)		NR
19		11,368 (100.0)		2522 (22.2)		5317 (46.8)		4328 (38.1)
20	NR			NR				
21	27 (24.1)		63 (56.2)					
22		0 (0.0)		80 (31.6)		NR		NR
23	199 (86.5)		106 (46.1)		230 (100.0)			
24	59 (44.4)		NR		133 (100.0)		NR	
25	79 (100.0)		58 (73.4)		79 (100.0)		46 (58.2)	
Studies in children								
26	0 (0.0)		66 (11.1)		586 (98.8)			
27		0 (0.0)		8 (5.8)		NR		NR
28		12,877 (100.0)		650 (5.0)		3847 (29.9)		6722 (52.2)
29		7 (15.6)		NR		NR		NR
30		0 (0.0)		26 (11.1)		NR		NR
31	NR		NR		72 (100.0)		NR	
32		145 (51.2)		24 (8.4)		NR		NR
33		0 (0.0)		25 (5.0)		NR		NR
34	0 (0.0)	0 (0.0)	NR	NR	NR	NR	NR	NR

Table A (2) | Patient characteristics and clinical characteristics (*continued*)

Number	OHCA (%)		Initial shockable rhythm (%)		Witnessed (%)		Bystander CPR (%)	
35	0 (0.0)		19 (12.9)		NR		NR	
36	NR	NR	NR	NR	NR	NR	NR	NR
37		0 (0.0)		18 (5.7)		261 (83.1)		NR
38	NR		NR		NR		NR	

Number	OHCA (%)		Initial shockable rhythm (%)		Witnessed (%)		Bystander CPR (%)	
	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
Studies in adults and children								
39	0 (0)	0 (0)	NR	NR	NR	NR	NR	NR
40		0 (0)		22 (24.4)		NR		89 (97.8)
41	NR		NR		NR		NR	
42	3 (12.0)							

Table A (3) | Patient characteristics and clinical characteristics

Number	ROSC (%)		Low flow time (min)	
	ECPR	CCPR	ECPR	CCPR
Studies in adults				
1		7312 (26.8)		30.0 (90th% 10.0-50.0)
2	NR	NR	60.0 (1.0)	35.0 (1.0)
3	131 (97.0)		50.0 (16.0-150.0)	
4	43 (100.0)	12 (52.2)	59.7 (34.1)	49.4 (34.6)
5		237 (53.2)		NR
6		NR		NR
7	NR		121.0 (55.0-192.0)	
8		31,198 (48.5)		17.0 (10.0-26.0)
9		2633 (46.0)		ROSC: 15.1 (8.4-22.4) no ROSC 27.0 (19.0-35.0)
10	NR		51.0 (35.0), 40.0 (20.0-70.0)	
11	44 (80.0)	212 (47.7)	62.0 (47.0-89.0)	35.0 (21.0-50.0)
12	NR		51.0 (37.0-80.0)	
13	NR		49.6 (13.4)	
14		32,185 (11.4)		NR
15	NR		47.0 (41.0-57.0)	
16	NR		74.0 (60.5-90.0)	
17		NR		survivors mean 12.6 non survivors mean 23.9
18		NR		6 (2-18)
19		4023 (10.8)		20 (12-27.3)
20		188 (53.9)		
21	108 (96.4)		46.0 (35.0-57.0)	
22		141 (55.7)		30.7 (range 5-220)
23			OHCA 67.5 (30.6) IHCA 44.4 (24.7)	
24	NR		59.6 (5.0)	
25	NR		45.0 (40.0-56.5)	
Studies in children				
26	NR		48.0 (28.0-70.0)	
27		82 (59.8)		mean 20.0
28		NR		NR
29		31 (68.9)		NR
30		171 (73.1)		NR
31	NR		60.0 (42.0-80.0)	
32		171 (60.4)		NR

Table A (3) | Patient characteristics and clinical characteristics (*continued*)

Number	ROSC (%)		Low flow time (min)	
33		349 (69.5)		NR
34	NR	NR	NR	NR
35	NR		closed chest 37 (22-51), open chest 53 (36.5-68.5)	
36	NR	56 (70.9)	50.0 (range: 5.0-105.0)	8.0 (range 1.0-62.0)
37		203 (64.6)		10.0 (3.0-30.0)
38	NR		NR	

Number	ROSC (%)		Low flow time (min)	
	ECPR	CCPR	ECPR	CCPR
Studies in adults and children				
39	33 (91.7)	219 (63.3)	70.5 (32.5)	NR
40		45 (49.5)		NR
41	NR		survivors 40.1 (18.9) non survivors 56.2 (30.0)	
42			30.0 (16.3-54.5)	

Table B | Modified Newcastle-Ottawa Quality assessment scale; based on primary outcome, measure is short-term survival

		Selection (4)				Comparability (2)		Outcome (3)				
Number	**Study**	1. Repre-sen-tativeness of exposed cohort	2. Selection of non-exposed cohort (selected from same cohort)	3. Ascertain-ment of exposure (secure record / structured interview)	4. Demon-stration that outcome of interest was not present at start of study	5. Comparabil-ity of cohorts on the basis of design or analysis controlled for confounders	6. Study propensity matched cohorts	7. Assessment of outcome (independent blind/record linkage	8. Follow-up long enough for out-come to occur?	9. Adequacy of follow up (>80% FU of cohort(s))	**Overall score (max. 9)**	**Overall score (qual-ity)**
Studies in adults												
1	Adnet	x	-	x	-	-	-	x	x	x	4	fair
2	Bartos	x	-	x	-	x	x	x	x	x	7	good
3	Chen	x	-	x	-	-	-	x	x	x	5	fair
4	Chou	-	x	x	-	x	-	x	x	x	6	fair
5	Dumot	x	-	x	-	-	-	x	x	x	5	fair
6	Ferguson	x	-	x	-	-	-	x	x	x	5	fair
7	Fjolner	x	-	x	-	-	-	x	x	x	5	fair
8	Goldberger	x	-	x	-	-	-	x	x	x	5	fair
9	Grunau	x	-	x	-	-	-	x	x	x	5	fair
10	Haneya	x	-	x	-	-	-	x	x	x	5	fair
11	Kim	x	x	x	-	-	x	x	x	x	7	good
12	Mandigers	x	-	x	-	-	-	x	x	x	5	fair
13	Murakami	x	-	x	-	-	-	x	x	x	5	fair
14	Nagao	x	-	x	-	-	-	x	x	x	5	fair
15	Otani	x	-	x	-	-	-	x	x	x	5	fair
16	Park	x	-	x	-	-	-	x	x	x	5	fair

Table B | Modified Newcastle-Ottawa Quality assessment scale; based on primary outcome, measure is short-term survival (*continued*)

		Selection (4)				Comparability (2)		Outcome (3)				
Number	**Study**	1. Repre-sen-tativeness of exposed cohort	2. Selection of non-exposed cohort (selected from same cohort)	3. Ascertain-ment of exposure (secure record / structured interview)	4. Demon-stration that outcome of interest was not present at start of study	5. Comparabil-ity of cohorts on the basis of design or analysis controlled for confounders	6. Study propensity matched cohorts	7. Assessment of outcome (independent blind/record linkage	8. Follow-up long enough for out-come to occur?	9. Adequacy of follow up (>80% FU of cohort(s))	**Overall score (max. 9)**	**Overall score (qual-ity)**
17	Pionkowski	-	-	x	-	-	-	x	x	x	5	fair
18	Pound	x	-	x	-	-	-	x	x	x	5	fair
19	Reynolds	x	-	x	-	-	-	x	x	x	5	fair
20	Rosenberg	x	-	x	-	-	-	x	x	x	5	fair
21	Siao	x	-	x	-	-	-	x	x	x	5	fair
22	Valentin	x	-	x	-	-	-	x	x	x	5	fair
23	Wang	x	-	x	-	-	-	x	x	x	5	fair
24	Wengenmayer	x	-	x	-	-	-	x	x	x	5	fair
25	Yukawa	x	-	x	-	-	-	x	x	x	5	fair
Studies in children												
26	Bembea	x	-	-	-	-	-	x	x	x	4	fair
27	Ganesan	x	-	x	-	-	-	x	x	x	5	fair
28	Goto	x	-	-	-	-	-	x	x	x	4	fair
29	Innes	x	-	x	-	-	-	x	x	x	5	fair
30	Kalloghlian	x	-	x	-	-	-	x	x	x	5	fair
31	Kramer	x	-	-	-	-	-	x	x	x	4	fair

Table B | Modified Newcastle-Ottawa Quality assessment scale; based on primary outcome, measure is short-term survival (*continued*)

		Selection (4)				Comparability (2)		Outcome (3)				
Number	**Study**	1. Repre-sen-tativeness of exposed cohort	2. Selection of non-exposed cohort (selected from same cohort)	3. Ascertain-ment of exposure (secure record / structured interview)	4. Demon-stration that outcome of interest was not present at start of study	5. Comparabil-ity of cohorts on the basis of design or analysis controlled for confounders	6. Study propensity matched cohorts	7. Assessment of outcome (independent blind/record linkage	8. Follow-up long enough for out-come to occur?	9. Adequacy of follow up (>80% FU of cohort(s))	**Overall score (max. 9)**	**Overall score (qual-ity)**
32	Lopez	x	-	x	-	-	-	x	x	x	5	fair
33	Lopez	x	-	x	-	-	-	x	x	x	5	fair
34	Matos	x	x	-	x	-	-	x	x	x	6	fair
35	Meert	x	-	x	-	-	-	-	-	x	3	poor
36	Morris	x	-	x	x	-	-	x	x	x	6	fair
37	Rathore	x	-	x	-	-	-	x	x	x	5	fair
38	Sivarajan	x	-	x	-	-	-	x	x	x	5	fair
Studies in adults and children												
39	Chen	x	-	x	-	-	-	x	x	x	5	fair
40	Hendrick	x	-	x	-	-	-	x	x	x	5	fair
41	Shinn	x	-	x	-	-	-	x	x	x	5	fair
42	Younger	-	-	x	-	-	-	x	x	x	4	fair

Table C | Summary of included studies

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
1	Adnet (8)	2017	descriptive	27,301	2011-2015	Patients of any age with OHCA and with involvement of mobile medical team	Not reported	30-days	30-day survival without neurologic sequelae	incidence of ROSC and death with ending of CPR
2	Bartos (52)	2020	case-control	133	2015-2019	ECPR: (1) 18-75 years of age, (2) OHCA of presumed cardiac origin, (3) initial rhythm of VF/VT, (4) received 3 direct current shocks for VF/VT without POSC or shock resulting in ongoing pulseless electrical activity or asystole, (5) received amiodarone 300mg, (6) body habitus accommodating a Lund University Cardiac Arrest System automated CPR device, (7) estimated transfer time to cardiac catherisation laboratory of <30 minutes	NR	6 months	Neurological favourable survival at hospital discharge	Metabolic changes in prolonged resuscitation

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
				654		CCPR: all patients 18-75 years of age included in the ALPS trial (non-traumatic OHCA, shock-refractory VF or pulseless VT after at least 1 shock and vascular access) enrolled in the amiodarone arm for whom data on duration of CPR and outcome were available	NR	hospital stay	Neurological favourable survival at hospital discharge	Not reported
3	Chen (22)	2008	descriptive	135	1994-2005	Patients between 18-75 years who underwent CPR for longer than 10 minutes for an IHCA with cardiac origin	CPR for less than 10 minutes, age over 75 years, previously known severe irreversible brain damage, terminal malignancy, traumatic origin with uncontrolled bleeding, non-cardiac arrest, signed 'do not attempt resuscitation'	5 years	Survival to hospital discharge	30-day and 1 year survival

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
4	Chou (23)	2014	case-control	66	2006-2010	All patients, age >18 years and sudden IHCA due to AMI at ED followed by CPR for more than 10 minutes	Age ≤ 18 years, terminal malignancy, previously known severe irreversible brain damage, cardiac arrest due to diagnosis other than AMI, CPR with ROSC within 10 minutes, signed 'do not attempt resuscitation' documents	hospital stay	Survival	Risk factors related to survival to hospital discharge
5	Dumot (24)	2001	descriptive	445	1994-1995	Age≥ 18 years, adherence to the advanced cardiac life support protocol, excepting intubation if it was not deemed necesary, chest compressions, and no limitation of resuscitation efforts (because of DNR)	Not reported	hospital stay	Survival immediately after resuscitation, at 24 hours, at 48 hours, and at hospital discharge	Not reported
6	Ferguson (25)	2008	descriptive	256	2001-2005	All patients with in hospital CPR efforts	Surgical and obstretics/ gynecology patients	6 months	Survival after hospital discharge	Not reported

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
7	Fjolner (46)	2017	descriptive	21	2011-2015	Patients ≥ 18 years with refractory, normothermic OHCA treated with ECPR. Patients with witnessed cardiac arrest who received immediate bystander and EMS CPR	>10 minutes delay until CPR or unwitnessed arrest, asystole or PEA, ETCO2<1.3kPa or low-flow duration >100 minutes, no heart movement at echocardiogram with adrenaline and pacemaker	hospital stay	Survival to hospital discharge with cerebral performance category of 1 and 2 at hospital discharge	Not reported
8	Goldberger (26)	2012	descriptive	64,339	2000-2008	Patients ≥ 18 years with index IHCA due to pulseless VT or VFm PEA or asystole	Patients treated in hospitals that reported their data less than 6 months, cardiac arrests of less than 2 minutes	hospital stay	Immediate survival with ROSC during cardiac arrest (at least 20 minutes) and survival to hospital discharge	Assesing wheter increased duration of resuscitation attempt results in worse neurological status
9	Grunau (28)	2018	descriptive	5674	2007-2011	Patients ≥ 18 years with non-traumatic OHCA treated by EMS	ROSC prior to EMS resuscitative attempt or if missing data precluded the a priori planned statistical analysis	hospital stay	Survival to hospital discharge	Favourable neurological outcome, defined as a CPC of 1-2

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
10	Haneya (48)	2012	descriptive	85	2007-2012	Patients ≥ 18 years with cardiac arrest receiving ECPR using percutaneous ECLS	Chest compressions not initiated within 10 minutes of arrest, estimated transport time more than 30 minutes, and total arrest time > 90 minutes	hospital stay	Survival to hospital discharge	Not reported
11	Kim (13)	2014	cohort	499	2006-2013	All ECPR patients, aged ≥18 years with sudden cardiac arrest with presumed correctable causes. Witnessed cardiac arrest with or without bystander CPR, or no-flow time was expected to be short, even for unwitnessed arrests.	Contra-indications ECPR: cardiac arrest due to a clearly uncorrectable cause, terminal illness or malignancy, suspected or confirmed traumatic origin of arrest, and no informed consent from the family	3 months	Good neurological outcome (CPC 1-2) at 3 months post cardiac arrest	24-hour survival rate, survival to discharge, and survival rate at 3 months post arrest
12	Mandigers (56)	2021	descriptive	84	2010-2020	All patients treated with ECMO who received ECPR	All patients with return of spontaneous circulation (ROSC) before ECPR initiation	hospital stay	Recovery of consciousness	ECMO survival, ICU-survival, hospital survival, and cause of death

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
12	Murakami (53)	2020	descriptive	85	2010-2015	(1) age <75 years, (2) presumed cardiac origin, (3)collapse witnessed by a bystander or reliable report of estimated collapse time, (4) refractory ventricular fibrillation that failes to respond to conventional CPR before arrival at the hospital	(1) age≥ 76 years, (2) cardiac tamponade caused by aortic dissection, (3) non-cardiac origin, (4) known poor prognosis or terminal malignancies	30-days	30-day neurological outcome using Glasgow-Pittsburgh Cerebral Performance Categories	Not reported
13	Nagao (35)	2016	descriptive	241,423	2005-2012	Adult patients with bystander-witnessed OHCA in whom EMS responders performed prehospital resuscitation care and who were transported to the hospital	Age <18 years, cardiac arrest after EMS responder arrival, unwitnessed OHCA, unidentified witness status, unidentified initial cardiac arrest rhythm, unidentified bystander resuscitation status, and a 'do not resuscitate' order.	30-days	Favorable 30-day neurological outcome (CPC 1-2)	Pre-hospital ROSC and 30-day survival

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
14	Otani (36)	2018	descriptive	135	2009-2017	Patients ≥ 16 years admitted to the hospital due to witnessed OHCA and which were resuscitated with ECPR	Patients with a 'do not attempt resuscitation' order, no ingormed consent, existing terminal illess, exogenous cause of arrest, or pericarial effusion and acute aortic dissection as suspected cause of the arrest	hospital stay	Favourable neurological outcomes (CPC 1-2) at hospital discharge	Not reported
16	Park (51)	2019	descriptive	140	2013-2016	All EMS assessed and bystander or EMS witnessed patients with OHCA of presumed cardiac aetiology whit age 15 years or older and received ECPR	In case of missing information on time from arrest to ECPR	hospital stay	Survival to hospital discharge	Not reported
17	Pionkowski (37)	1983	descriptive	565	1978-1982	Initial rhythm ventricular fibrillation	pediatric, trauma, poisoning, or drowning cases	hospital stay	Survival	Not reported

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
18	Pound (54)	2020	descriptive	152	2017-2018	Adults (≥ 18 years old) admitted as acute care hospital in-patient and exoeriencing IHCA	Patients with 'not for resuscitation' order prior to IHCA, cardiac arrhythmia requiring electrical cardioversion but no external cardiac compressions. Non ward-based cardiac arrests.	hospital stay	Functional outcome at hospital discharges measured using the modified Rankin Scale	In-hospital mortality and independence with activities of daily living at hospital discharge measudred using the Katz-ADL
18	Reynolds (39)	2016	descriptive	11,368	2007-2010	Patients ≥ 18 years suffering non-traumatic OHCA who receive defibrillation and/or chest compressions	Patients with a 'do not attempt resuscitation' order, trauma, known prisoners, known pregnancy, persons bearing a designated indicator of their having 'opted out' of the trial as required by local IRBs, tracheostomy, CPR with mechanical compression device, ventilated with a mechanical device, or initial treatment by a non-ROC EMS agency/provider with no agreement in place to obtain relevant EMS data	hospital stay	Survival to hospital discharge with favourable functional status (mRS 0-3)	Not reported

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
19	Rosenberg (40)	1993	descriptive	336	1988-1989	All patients having cardiopulmonary arrest with resuscitation occurring in the hospital	Patients with seizures, syncope, or isolated respiratory failure without accompanying hemodynamic compromise	hospital stay	Survival to hospital discharge	Not reported
21	Siao (58)	2020	descriptive	112	2012-2017	age 18–75 years; cardiac arrest presumed to be of cardiac origin; C-CPR initiated for cardiac arrest within 5 min (no-flow time ≤ 5 min); and refractory cardiac arrest defined as failure to achieve return of spontaneous circulation (ROSC) after at least 10 min of C-CPR	if the time from cardiac arrest onset to C-CPR activation was prolonged or unknown. They were also excluded if they had severe head trauma, acute active bleeding, severe sepsis, terminal cancer, or any history of severe neurological deficits (including dementia, ischemic stroke, intracranial hemorrhage, and bedridden state)	six months	Survival	Not reported

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
20	Valentin (49)	1995	descriptive	253	1989-1991	IHCA patients, including patients who developed cardiac arrest during admission procedures as well as patients admitted to the coronary care unit	OHCA patients and patients in whom cardiac arrest occurred while admitted to the ICU	hospital stay	Survival to hospital discharge	Not reported

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
21	Wang (43)	2014	cohort	230	2007-2012	Patients ≥ 16 years with witnessed OHCA with possible cause of cardiac origin and unknown origin excluding the exclusion criteria, unconsciousness, dilated pupil during CPR, CPR for longer than 10 minutes without ROSC under active CPR	Age >80 years or <16 years, terminal stage malignancy, pre-existing multi-organ dysfunction, ventilator-dependent > 3 months, bed-risen > 3 months, nor self-independent, acute/active intracranial haemorrhage or infarct or severe head injury, traumatic origin, uncontrollable bleeding, arrest without active CPR, non-witnessed cardiac arrest, uncontrolled infection, Charlson score >7, ROSC for 20 minutes after resuscitation without repeated collapse, conscious patient, patient with 'DNR' order	hospital stay	Survival to hospital discharge	Favourable neurological outcome, defined as a CPC of 1-2
22	Wengenmayer (10)	2017	cohort	133	2010-2016	All patients treated with VA-ECMO due to cardiac arrest	Not reported	hospital stay	Survival to hospital discharge	Not reported

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
23	Yukawa (45)	2017	descriptive	79	2011-2015	Patients ≥ 18 with witnessed OHCA who were brought to the ED and which were resuscitated with ECPR	Not reported	hospital stay	Survival to hospital discharge with good neurological outcomes (CPC 1-2)	Not reported
28	Bembea (20)	2013	descriptive	593	2000-2014	Patients less than 18 years old with an IHCA who underwent ECMO cannulation during the CPR event	Newborns with cardiac arrest in the delivery room and patients with missing data on mortality were excluded.	hospital stay	Mortality prior to hospital discharge	Neurologic outcome at hospital discharge and discharge destination among survivors
29	Ganesan (47)	2018	descriptive	137	2012-2014	All children from day one to 12 years of age developed in-hospital cardiac arrest in paediatric general ward, Emergency and PICU	Children with cardiac arrest within six hours of admission in paediatric emergency care, preterm neonates, children with terminal illness receiving compassionate care, children in whom CPR is not initiated or children with brain death	hospital stay	Survival to hospital discharge	Not reported
30	Goto (27)	2016	descriptive	12,877	2005-2012	All paediatric patients (<18 years of age) for whom resuscitation had been performed after OHCA	Not reported	30-days	30-day survival with favorable neurological outcome	30-day survival

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
31	Innes (50)	1993	descriptive	45	1990-1991	All resuscitation attempts	Not reported	1 year	Initial succes (ROSC) and one month survival	Not reported
32	Kalloghlian (30)	1998	descriptive	234	1989-1992	All paediatric patients less than 13 years of age who received external cardiac massage because of clinically absent central pulses. Patients in the study were hospitalized in general paediatric wards, or in one of the intensive care units	Patients who did not require ECM as part of their resuscitation and patients resuscitated in the Emergency Room, the Operating Rooms and the Cardiac Catheter Laboratory were also excluded. If patients had more than one record, only data from the first record was included.	hospital stay	Initial survival (ROSC) and survival to hospital discharge	Not reported
31	Kramer (55)	2020	descriptive	72	2005-2016	All children less than 18 years old that received ECPR	Patients with return of spontaneous circulation of any duration before the initiation of ECMO flow	edian 4.1 years (3.7–6.1 yr)	Survival to hospital discharge	Neurological outcome
33	Lopez (32)	2004	descriptive	283	1998-1999	Patients aged from 7 days to 18 years if they had presented in respiratory arrest or cardiac arrest	Not reported	1 year	Survival to hospital discharge and 1-year survival	
34	Lopez (31)	2013	descriptive	502	2007-2009	Children aged from 1 month to 18 years who suffered IHCA	Not reported	hospital stay	Survival to hospital discharge	Neurological status at hospital discharge

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
35	Matos (33)	2013	descriptive	3419	2000-2009	All index pulseless IHCA events occurring in patients <18 years of age for which at least 1 minute of chest compressions was provided. Also patients in other locations (outpatient clinics within the hospital, visitors, and inpatients of rehabilitation, skilled nursing, and mental health facilities attached to study hospitals)	Patients in whom the event began out of the hospital or in the neonatal intensive care unit, delivery room, or nursery. Patients with illness categories of newborn, obstetric, or other illnesses	hospital stay	Survival to hospital discharge	Return of spontaneous circulation >20 minutes, 24-hour survival, and survival to discharge with favourable neurological outcome

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
35	Meert (57)	2019	descriptive	147	2009-2015	Children were more than 48 hours and less than 18 years old, had an in-hospital cardiac arrest with chest compressions for greater than or equal to 2 minutes, and required mechanical ventilation after return of circulation. Receipt of ECPR defined as ECMO initiation during active chest compressions or before sustained return of spontaneous circulation greater than 20 minutes was achieved	Inability to be randomized within 6 hours of return of circulation, a Glasgow Coma Scale motor score of 5 or 6 (24), and a decision to withhold aggressive treatment.	1 year	Survival	Not reported
36	Morris (34)	2004	cohort	145	1995-2002	All children who were resuscitated from cardiac arrest during active chest compressions by means of venoarterial ECMO	Patients who were resuscitated at the neonatal ICU	hospital stay	Survival to hospital discharge	Not reported

Table C | Summary of included studies (*continued*)

No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
38	Sivarajan (42)	2011	descriptive	37	1990-2006	All children with cardiac disease who required ECMO	All patients placed on veno-venous ECMO, all patients placed on ECMO for primary respiratory or septic indications and all patients with congenital diaphragmatic hernia	2 year	Survival to hospital discharge	Not reported
24	Chen (21)	2016	descriptive	382	2012	All adult and paediatric patients who received an in-hospital resuscitation attempt after cardiac arrest	OHCA, patients with a DNR order, and IHCAs occurring in visitors, outpatients, or hospital employees	hospital stay	Immediate survival with ROSC and survival to hospital discharge	CPC at hospital discharge (a favourable neurological status was defined as a score of 1 or 2)
25	Hendrick (29)	1990	descriptive	90	1986-1988	All patients resuscitated in the general wards in which there was a cardiopulmonary arrest at the arrival of the team	Resuscitation performed in the cardiac care and intensive care units, the emergency department, and the operation theatres	1-18 months	Immediate survival (ROSC) and survival to hospital discharge	Not reported

Table C | Summary of included studies (*continued*)

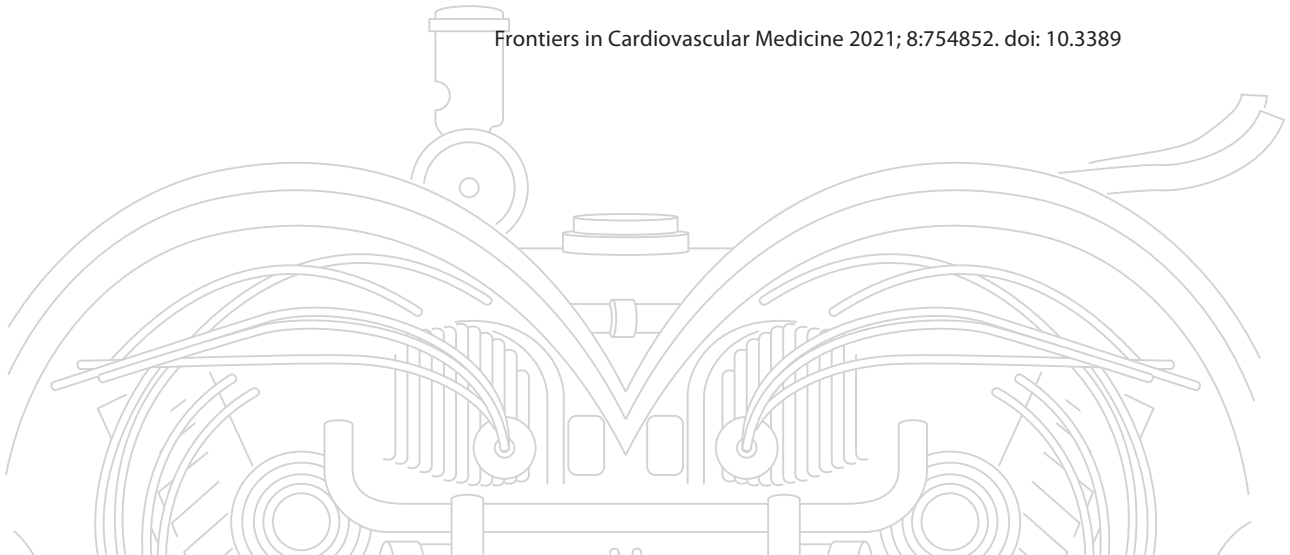
No	Study	Publication year	Study design	Sample size	Inclusion period	Inclusion criteria	Exclusion criteria	Follow-up period	Primary outcome	Secondary Outcome
26	Shinn (41)	2009	descriptive	50	2004-2006	All patients treated with percutaneous cardiopulmonary support owing to cardiac arrest and intractable cardiogenic shock with imminent cardiac arrest or respiratory failure	Not reported	hospital stay	Weaning and survival to hospital discharge	Not reported
27	Younger (44)	1999	descriptive	23	1991-1998	Patients in cardiac arrest or immediately post-cardiac arrest with poor systemic perfusion were considered candidates for therapy. Patient referrals were solicited from the ED and inpatient services. Patients in which the ECPR team was consulted	Relative contraindications included arrest time >30 minutes or profound metabolic acidosis (pH < 7.0).	hospital stay	Survival to hospital discharge or successful placement of ventricular assist device as a bridge to cardiac transplantation	Not reported

Chapter 5

Monitoring mitochondrial partial oxygen pressure during cardiac arrest and extracorporeal cardiopulmonary resuscitation: An experimental pilot study in a pig model

Loes Mandigers, Jan-Steffen Pooth, Mark Wefers-Bettink, Corstiaan A. den Uil, Domagoj Damjanovic, Bert Mik, Sam Brixius, Diederik Gommers, Georg Trummer, Dinis dos Reis Miranda

Frontiers in Cardiovascular Medicine 2021; 8:754852. doi: 10.3389



ABSTRACT

Introduction Ischemia and reperfusion are crucial in determining the outcome after cardiac arrest and can be influenced by extracorporeal cardiopulmonary resuscitation (ECPR). The effect of ECPR on the availability and level of oxygen in mitochondria remains unknown. The aim of this study was to find out if skin mitochondrial partial oxygen pressure ($mitoPO_2$) measurements in cardiac arrest and ECPR are feasible and to investigate its course.

Materials and Methods We performed a feasibility test to determine if skin $mitoPO_2$ measurements in a pig are possible. Next, we aimed to measure skin $mitoPO_2$ in 10 experimental pigs. Measurements were performed using a cellular oxygen metabolism measurement monitor (COMET), at baseline, during cardiac arrest, and during ECPR using the controlled integrated resuscitation device (CIRD).

Results The feasibility test showed continuous $mitoPO_2$ values. Nine experimental pigs could be measured. Measurements in six experimental pigs succeeded. Our results showed a delay until the initial spike of $mitoPO_2$ after ECPR initiation in all six experimental tests. In two experiments (33%) $mitoPO_2$ remained present after the initial spike. A correlation of $mitoPO_2$ with mean arterial pressure (MAP) and arterial partial oxygen pressure measured by CIRD (CIRD-PaO_2) seemed not present. One of the experimental pigs survived.

Conclusions This experimental pilot study shows that continuous measurements of skin $mitoPO_2$ in pigs treated with ECPR are feasible. The delay in initial $mitoPO_2$ and discrepancy of $mitoPO_2$ and MAP in our small sample study could point to the possible value of additional measurements besides MAP to monitor the quality of tissue perfusion during cardiac arrest and ECPR.

Keywords: heart arrest, cardiac arrest, extracorporeal cardiopulmonary resuscitation, mitochondrial oxygen pressure, circulation monitoring

INTRODUCTION

In cardiac arrest, the duration of ischemia is an important determinant for survival and neurological outcome. [1, 2] In order to shorten this ischemic period during cardiac arrest, extracorporeal cardiopulmonary resuscitation (ECPR) can be used to recover circulation and effective oxygen transport. The possible beneficial effect of ECPR on neurologically favorable survival has already been studied previously. [3] However, the best treatment protocol of ECPR regarding ECPR settings is still unknown.

To determine if the recovery of circulation and oxygen delivery using ECPR are sufficient, we measured oxygen in the mitochondria, as final destination of oxygen. After all, mitochondria are important for generating energy, using oxygen, for cellular processes and maintaining life. [4, 5] Protoporphyrine IX (PpIX) is an endogenously present porphyrin in the mitochondria, which can be enhanced by administrating 5-aminolevulinic acid hydrochloride (ALA) crème. [6] The subcellular distribution of PpIX in ALA stimulated cells has been studied using wide-field fluorescence microscopy.[7] Previous research has shown the possibilities of measuring partial oxygen pressure (PO_2) in the mitochondria by PpIX using its oxygen-dependent delayed fluorescence. [7-10] To confirm that this delayed fluorescence truly measures inside the mitochondria, a previous study compared photobleaching (a contrast enhancement technique for PpIX) to MitoTracker Green (a method to identify mitochondria). This comparison showed a high degree of co-localization. [7] This confirmed that, for a time window of several hours after ALA administration, PpIX measurements with delayed fluorescence corresponds to a mitochondrial localization. [7] This method of measuring mitochondrial PO_2 ($mitoPO_2$) has also been validated to perform well in the skin. [11] In addition, the possibility to perform continuous $mitoPO_2$ measurements is shown in adults by Ubbink et al. [10] and in newborns by Costerus et al. [12].

The primary aim of this study is to find out if continuous measurements of skin $mitoPO_2$ in a pig are feasible and what the course of this $mitoPO_2$ is during cardiac arrest and ECPR. The secondary aims are to investigate if there is a correlation between the course of $mitoPO_2$ and mean arterial pressure (MAP) and to identify the correlation between the course of $mitoPO_2$ and favorable neurological survival.

METHODS

Between November 2017 and September 2020, 11 male and female German landraces pigs (weight: 50.0-82.0 kg) were eligible for skin $mitoPO_2$ measurements. Continuous skin $mitoPO_2$ measurements in pigs with experimental settings of cardiac arrest treated with ECPR have not been performed before. In order to determine if these measurements

are possible to perform and feasible in our test set up we first performed a feasibility test in one pig. This test showed that continuous measurements in this set up was possible. Therefore, we selected 10 pigs to perform continuous skin mitoPO$_2$ measurements as experimental test group. Of these 10 experimental tests, one could not be performed due to technical failure before the start of the test.

All animals received humane care and were treated in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. [13] The experiments were performed in accordance with the rules and regulations of the German animal protection law and the animal care guidelines of the European Community. The experiments were performed in the University of Freiburg, a highly experienced animal lab performing many ECPR procedures in pigs, and approved by the committee for ethics of the University Hospital Freiburg, Freiburg, Germany (no.G-15/148).

Preparation of Tests

After premedication (20 mg/kg ketamine and 0.5 mg/kg midazolam) an intravenous (IV) access was placed, the pigs were sedated and paralyzed (3-4 mg/kg propofol and 0.2 mg/kg vecuronium), intubated, and mechanically ventilated. Continuous intravenous anesthesia consisted of the administration of 10-15 mg/kg/h propofol, 1-5 µg/kg/h fentanyl and 0.2-0.4 mg/kg/h vecuronium. In the pre-arrest period the core temperature we aimed for was 36-38°C. This temperature was measured by a nasal temperature sensor and in case of a low body temperature the pig was heated using a warming blanket.

In order to perform mitoPO$_2$ measurements, a part of the skin (~1 cm^2) was prepared. First, hair was removed by shaving, the skin was roughened, and then the skin was cleaned using sodium chloride (NaCL 0.9%) and ethanol (70%). The 20% ALA crème was prepared by mixing 400mg ALA (Fagron, Barsbüttel, Gemany) with 2g Lanettecrème I FNA (Teva Nederland BV, Haarlem NL). [6] To avoid photobleaching of PpIX by light, the applied ALA crème was directly covered by a plaster and by aluminium foil. The crème was placed 3h before the first measurement and during this waiting time it was continuously protected to light. [7, 11] Because of the use of a mechanical cardiopulmonary resuscitation (CPR) device and cannulation in the right groin and neck, we measured the mitoPO$_2$ in the left axilla/neck region. Five minutes before induction of arrest, the effect of the ALA crème was tested by compression of the sensor on the skin. [8, 10] When the measurements were finished, the skin was again covered to protect from light in order to protect it from burn lesions.

Test procedure

The protocols and set up of the feasibility test and the experimental tests were slightly different, we will describe the test procedures separately.

Feasibility test:

Ventricular fibrillation (VF) was induced by electrical stimulation via a Swan-Ganz catheter (Edwards Lifesciences Corp., Irvine, CA, USA). During 20 min of cardiac arrest, venous and arterial access was surgically generated via the right external jugular vein (23 Fr cannula) and the right common femoral artery (17 Fr cannula), respectively. In the period of cardiac arrest, mechanical ventilation was stopped and no life support was applied. After 20 min of cardiac arrest, ECPR was initiated with blood flow varying from 5.9-7.6 L/min. External defibrillation was performed in case of persisting VF. ECPR was weaned and stopped 60 min after initiation. If the animal could be weaned from ECPR, it was subsequently weaned from the ventilator and transferred to the animal facility after extubation. The pig was examined daily and neurological outcome was tested using a modified species-specific neurological deficit score (NDS). [14] This NDS ranges from 0 (normal) to 500 (brain death) and a favorable outcome was defined as NDS below 50. [14, 15] Euthanasia was performed in tabula in case the pig could not be weaned off extracorporeal circulation or invasive ventilation, in case the pig was expected to have inhumane suffering or prolonged death (an NDS of >200 at 24 h or an NDS of >120 at 48 h), and otherwise after 7 days. [15]

Experimental tests:

In the nine experimental tests, the ECPR implantation and induction of VF was the same as described at the feasibility test, except the timing of ECPR cannulation. In the experimental tests, this was already performed in the pre-arrest period. Next, after 5 min of VF, basic life support (BLS) was started with cardiopulmonary resuscitation (CPR) using a mechanical compression device (Corpuls CPR, GS Elektromedizinische Geräte G. Stemple GmbH, Kaufering, Germany) for 8 min. The next 22 min consisted of advanced life support (ALS), with additional administration of epinephrine every 4 min. After 35 minutes of cardiac arrest and CPR, ECPR was initiated with blood flow varying from 5.5 to 7.9 L/min and a 20ml bolus of 7.45% potassium was applied for rhythm conversion. During ECPR in case of persisting VF, the heart was electrically defibrillated. If the VF sustained after three defibrillations, amiodarone and lidocaine were administered. If needed, continuous norepinephrine was administered with an aimed MAP of 60-80 mmHg. For these 10 experiments the controlled automated reperfusion of the whole body (CARL) protocol with the controlled integrated resuscitation device (CIRD, 1.0 Resuscitec GmbH, Freiburg/Germany) was used. [15] ECPR was weaned around 120 min after initiation. This weaning consisted of slowly reducing the flow within 15-20 min until 1.5L/min If the pig displayed signs of sufficient circulation (i.e., arterial amplitude above 20 mmHg, MAP above 60 mmHg, and stable lactate measurements) ECPR was discontinued and surgically removed. All post ECPR care and neurologic outcome scoring was comparable to the feasibility test as described above.

MitoPO$_2$ measurements

The background of PpIX delayed fluorescence measurements is described in detail elsewhere. [7] In short, PpIX is the final precursor of heme and is synthesized inside the mitochondria. [7] When ALA crème is applied to the skin it enhances the endogenously present PpIX. The PpIX accumulates inside the mitochondria and possesses a triplet state, which reacts strongly with oxygen and therefore it can be used as an intramitochondrial oxygen sensor. [7] For this experiment we used the previously described cellular oxygen metabolism monitor (COMET, Photonics Healthcare B.V., Utrecht, The Netherlands) to measure mitoPO$_2$. [10] The effect of the ALA crème was tested with an oxygen-consumption measurement performed by applying pressure on the skin sensor. This pressure causes an occlusion of microcirculatory blood flow and therefore oxygen delivery to the mitochondria is stopped, resulting in a decrease of mitoPO$_2$. [8, 10] A decrease of mitoPO$_2$ to ≤5mmHg and a return to baseline values after release of the pressure on the skin sensor was defined as successful oxygen-consumption measurement. This measurement was performed at least two times before induction of cardiac arrest. During cardiac arrest and during ECPR mitoPO$_2$ was measured every minute and, on indication, more often with a maximum frequency of every second for 60 s.

Other measurements

Arterial PO$_2$ was measured via online blood gas sampling by the CIRD (CIRD-PaO$_2$). Systolic, diastolic, and mean arterial pressure were measured invasively via a carotid arterial cannula. For the feasibility test we will plot the mitoPO$_2$ and CIRD-PaO$_2$ in a graph. All outliers of >200 mmHg will be set at 200mmHg. The mitoPO$_2$ (in mmHg), CIRD-PaO$_2$ (in mmHg), and MAP (in mmHg) of the experimental tests will be plotted in graphs from baseline until discontinuation of ECPR flow, which will approximately be at 2.5-3.0 h after initiation of ECPR. Due to the small number of cases, the courses of these measured values cannot be compared using statistical testing. Therefore, the comparing of the graphs will be done by careful visual inspection.

RESULTS

Feasibility test

The feasibility test we performed, was to find out if skin mitoPO$_2$ measurements in a pig during cardiac arrest and ECPR were possible. As shown in Figure 1, mitoPO$_2$ of this case dropped after initiation of VF. When ECPR was initiated (after 20 min of VF), an initial spike in mitoPO$_2$ followed by a slow upslope was seen. After the initial spike, the level of mitoPO$_2$ remained high. This pig survived after ECPR weaning with a NDS at day 1 of 100,

at day 2 a NDS of 60, and the following days a NDS of 0. Seven days after the experiment, it was euthanized according to the protocol.

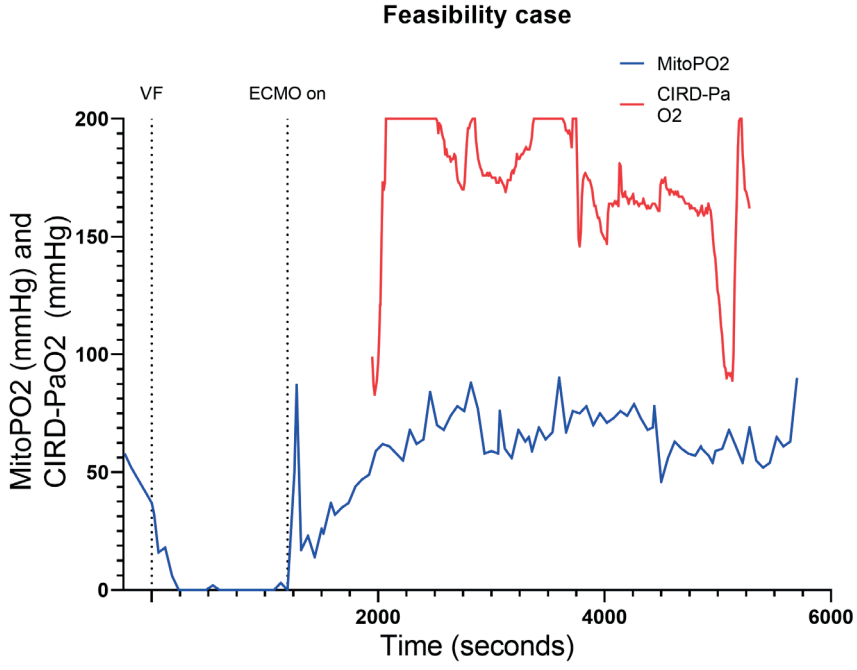


Figure 1 | Course of mitoPO2 and CIRD-PaO2 for the feasibility test. Course of mitoPO2 and CIRD-PaO2 in mmHg levels over time in seconds. VF, ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO2, arterial partial oxygen pressure measured by controlled integrated resuscitation device; mitoPO2, mitochondrial partial oxygen pressure.

Experimental tests

Of the nine experimental tests we performed, four had to be excluded. A detailed description of reasons for exclusion is found in Supplementary Appendix A. In short, in one experimental test the skin with ALA was exposed to too much light. In two other experimental cases we failed to perform the measurements continuously during the tests. The last experimental case could not be performed due to complication during preparation. Two of these experimental pigs were male and two female.

We included six (50.0-70.5kg) pigs in this experimental test group. The characteristics of the measurements of these pigs are reported in Table 1. Figures 2-4 show the course of mitoPO$_2$, CIRD-PaO$_2$, and MAP of the six experimental tests in separate graphs, from baseline (just before start of the cardiac arrest) until discontinuation of ECPR flow. In all pigs, directly after initiation of VF, the mitoPO$_2$ decreased rapidly. As shown in Table 2,

Table 1 | Individual characteristics of measurements in six experimental pigs

Case	1	2	3	4	5	6
Sex	Male	Male	Male	Male	Male	Male
Weight (kg)	50	54	59	62	70.5	70.5
Time: initiation of VF until first low mitoPO$_2$ (≤5mmHg) in seconds	26	23	13	31	60	64
Time: initiation ECPR until mitoPO$_2$ >5mmHg in seconds	1122	1829	1139	481	900	1008
Correlation of mitoPO$_2$ and CIRD-PaO$_2$	No	No	Yes	Yes	No	No
ECPR Survival	No	No	No	Yes, 2 days	No	No

Time initiation of VF until first low mitoPO2 is set as the time of initiation of VF until the first mitoPO2 measurement of ≤5mmHg. VF: ventricular fibrillation, mitoPO$_2$: mitochondrial partial oxygen pressure, BLS: basic life support, ALS: advanced life support, ECPR: extracorporeal cardiopulmonary resuscitation, CIRD-PaO$_2$: partial oxygen pressure measured by controlled integrated resuscitation device

the median time from initiation of VF until a mitoPO$_2$ of ≤5mmHg was 29 s (interquartile range, IQR 23-60 s). The median time from initiation of ECPR until first rise in mitoPO$_2$ above 5mmHg was 1066 s (i.e., 17 min and 46 s, IQR 900-1139 s).

In four of the six experimental tests (case 1, 2, 5, and 6), after initiation of ECPR the initial spike of mitoPO$_2$ did not result in persisting high mitoPO$_2$ values. In the other two experimental tests (case 3 and 4), after initiation of ECPR the initial spike of mitoPO$_2$ was followed by a continuous level of mitoPO$_2$ which approached baseline levels. There was no correlation between mitoPO$_2$, CIRD-PaO$_2$, and MAP in the tests without persisting mitoPO$_2$ values. In the two patients with continuous higher levels of mitoPO$_2$, comparing the correlation of mitoPO$_2$, CIRD-PaO$_2$, and MAP is complex. With careful visual inspection, the difference between the three values is smaller and seems somewhat related, especially in case 4. Case 3 could not be successfully weaned from ECPR due to technical problems. Case 4 survived after ECPR weaning. The NDS of this pig was 130 at day 1 and 2 and it was euthanized at day 2 due to humane reasons. All other cases could not be successfully weaned from the ECPR and died at termination of the experiment.

Table 2 | Summary of characteristics

Time: VF – low mitoPO$_2$ (≤5mmHg) in seconds	29 (23-60)
Time: initiation ECPR until mitoPO$_2$ >5mmHg in seconds	1066 (900-1139)
Correlation of mitoPO$_2$ and CIRD-PaO$_2$	2/6 cases (66.7%)
ECPR Survival	1/6 cases (16.7%)

The continues variables are presented as medians and interquartile ranges, the categorical variables are presented as number and percentage.

VF: ventricular fibrillation, mitoPO$_2$: mitochondrial partial oxygen pressure, BLS: basic life support, ALS: advanced life support, ECPR: extracorporeal cardiopulmonary resuscitation, CIRD-PaO$_2$: partial oxygen pressure measured by controlled integrated resuscitation device

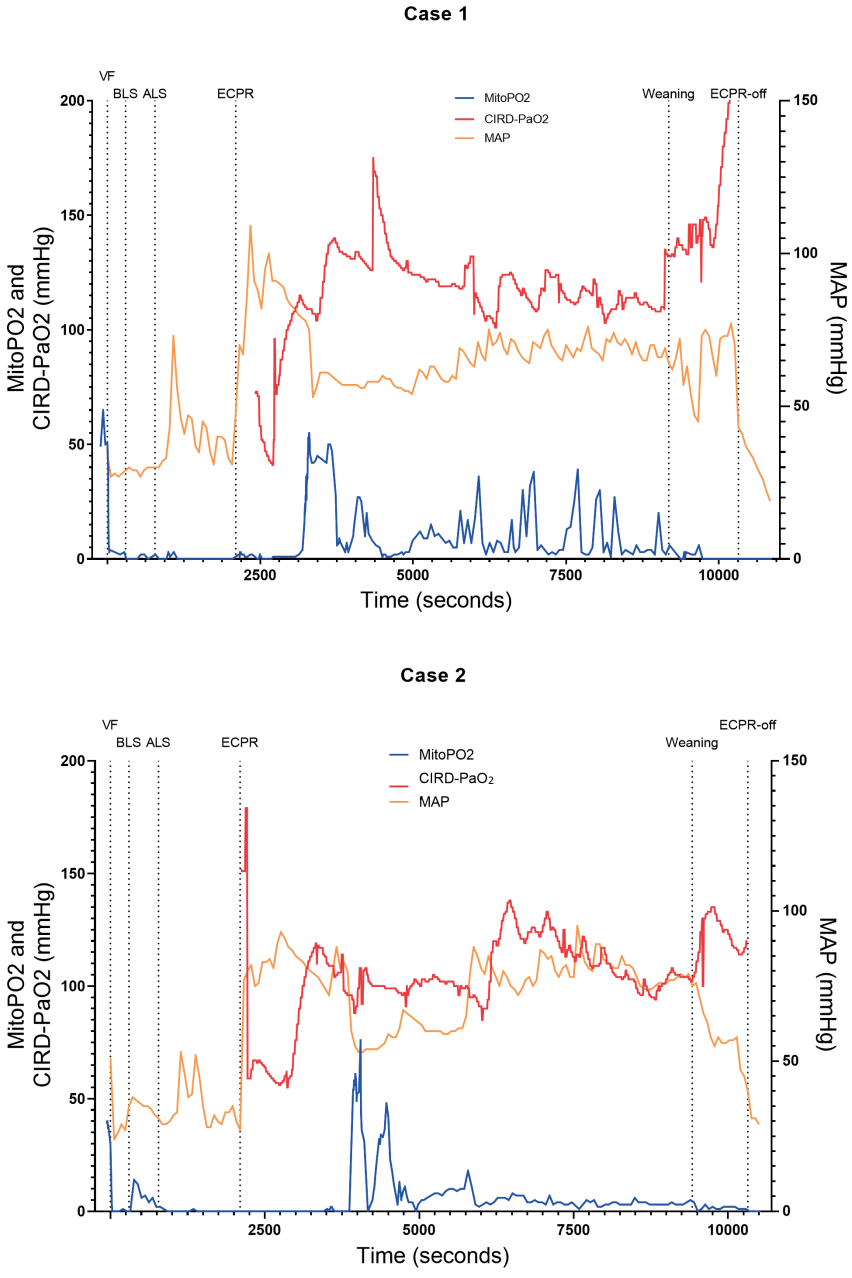


Figure 2 | Course of mitoPO2, CIRD-PaO2, and MAP for experimental tests case 1 and 2. Course of mitoPO2 and CIRD-PaO2 in mmHg levels at the left Y-axis and course of MAP in mmHg levels at the right Y-axis all over time in seconds. Case 1 at the above panel and case 2 at the below panel. VF, ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO2, arterial partial oxygen pressure measured by controlled integrated resuscitation device; mitoPO2, mitochondrial partial oxygen pressure.

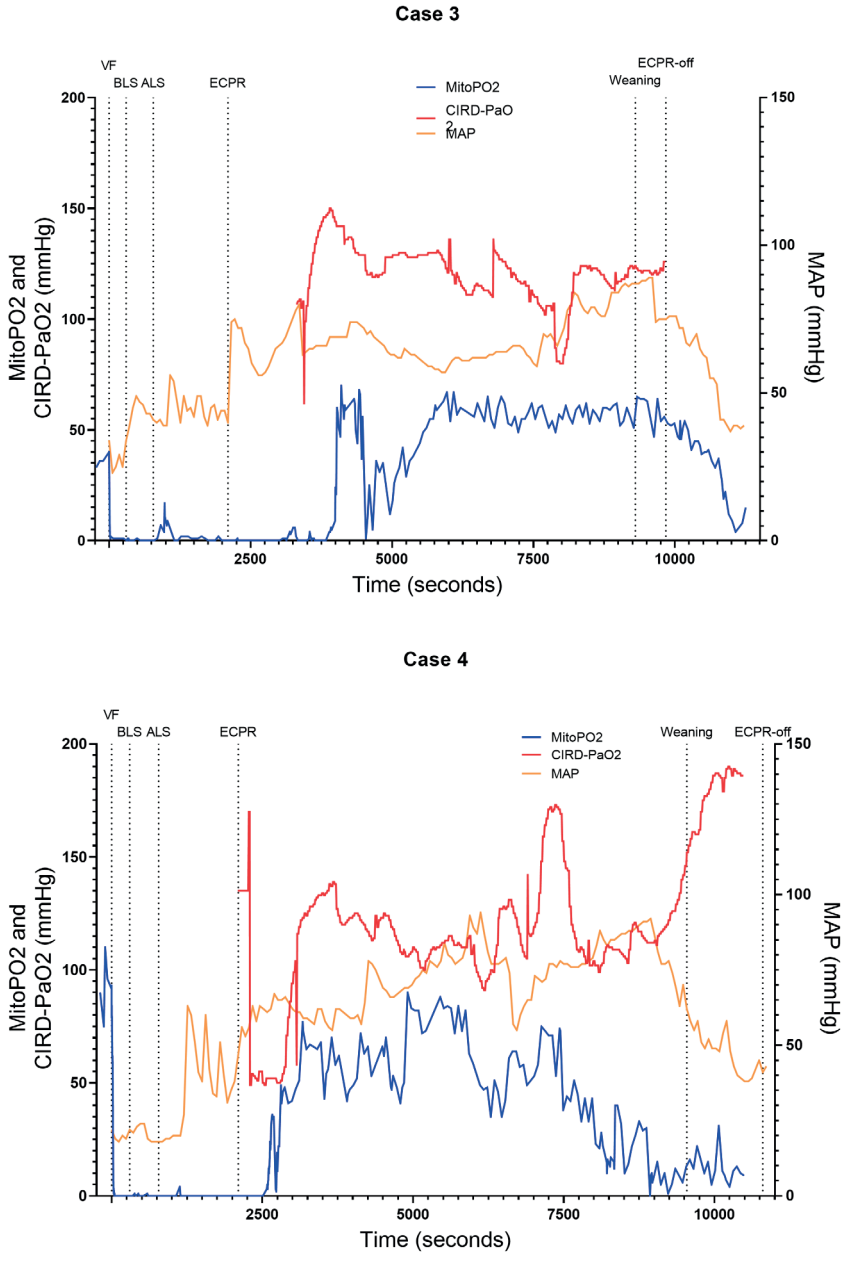


Figure 3 | Course of mitoPO2, CIRD-PaO2, and MAP for experimental tests case 3 and 4. Course of mitoPO2 and CIRD-PaO2 in mmHg levels at the left Y-axis and course of MAP in mmHg levels at the right Y-axis all over time in seconds. Case 3 at the above panel and case 4 at the below panel. VF, ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO2, arterial partial oxygen pressure measured by controlled integrated resuscitation device; mitoPO2, mitochondrial partial oxygen pressure.

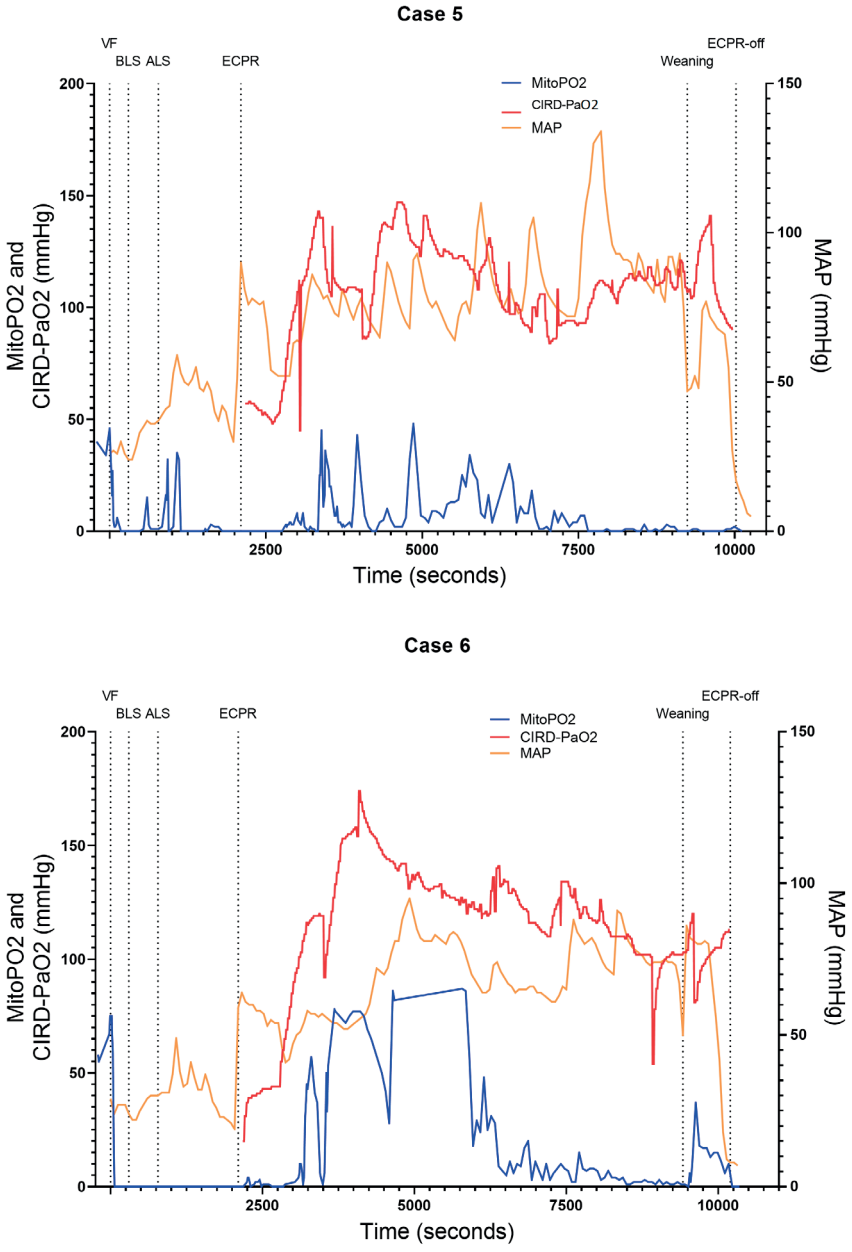


Figure 4 | Course of mitoPO2, CIRD-PaO2, and MAP for experimental tests case 5 and 6**.** Course of mitoPO2 and CIRD-PaO2 in mmHg levels at the left Y-axis and course of MAP in mmHg levels at the right Y-axis all over time in seconds. Case 5 at the above panel and case 6 at the below panel. VF, ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO2, arterial partial oxygen pressure measured by controlled integrated resuscitation device; mitoPO2, mitochondrial partial oxygen pressure.

DISCUSSION

In this study we showed that skin mitoPO$_2$ measurements in a pig during cardiac arrest and ECPR are feasible. In all six experimental tests we found a rapid decrease of mitoPO$_2$ after initiation of VF and a remarkably delayed increase in the initial measured mitoPO$_2$ after reperfusion via ECPR. In four of the six cases no continuously high mitoPO$_2$ values were present. However, in two of the cases mitoPO$_2$ remained near baseline levels after the initial spike. The course of mitoPO$_2$ in these two cases seemed correlated with CIRD-PaO$_2$ and MAP. One of these pigs survived, but with an unfavorable neurological outcome until 2 days after the experiment.

The rapid decrease of mitoPO$_2$ after initiation of VF was expected to be found, because of the immediate stop of oxygen delivery and uptake due to whole body ischemia. Harms et al. [8] showed a rapid decrease of mitoPO$_2$ as soon as oxygen delivery to the skin is stopped by performing local pressure to the skin sensor, which occludes the microvessels, in a rat experiment. Ubbink et al. [10] repeated this test in humans and they also found a rapid decrease in mitoPO$_2$ when applying local pressure. After initiation of VF in our tests, systemic blood flow stops and therefore there will be a rapid decrease in oxygen delivery. This disappearance of blood flow and oxygen delivery acts the same as the oxygen consumption tests performing pressure to occlude the microvessels. This demonstrates the close relationship of tissue perfusion and tissue oxygenation.

The delay of increase in mitoPO$_2$ after initiation of ECPR we found is most probably due to adrenaline administered during ALS according to the resuscitation guidelines. The possible effects of medication on mitoPO$_2$ has been shown before. Ubbink et al. [10] showed, as an incidental finding, that the initial vasoconstriction caused by clonidine decreased the skin mitoPO$_2$ values. There was no effect on capillary venous oxygen saturation, however the effect on mitoPO$_2$ and flow remained present for around 15 min. [10] Adrenaline stimulates the α1-receptors, among others, which causes vasoconstriction and centralization of blood flow. [16] The effect of adrenaline on mitoPO$_2$ values has not been shown before. However, Fries et al. [17] showed that administration of adrenaline caused a decrease in capillary blood flow which persisted after the achievement of return of spontaneous circulation (ROSC). Therefore, administration of adrenaline might explain the delay of increase in skin mitoPO$_2$ values.

Another explanation for the delay of increase in mitoPO$_2$ after initiation of ECPR could be centralization, where the skin as an end organ will be the last organ to regain flow. After initiation of ECPR, the macrocirculation (MAP and blood flow) is restored immediately. However, the exact timing of restoration of the microcirculation in different tissues is unknown. In cardiac arrest, arterial blood flow decreases to zero and during CPR it will remain lower than normal. [18] Therefore the reduced stimulation of the arterial baroreceptors will activate the sympathetic system. [19] This sympathetic system

will centralize the blood flow and causes vasoconstriction to preserve heart and brain function. [19] A hypothesis could be that when ECPR is initiated this vasoconstriction is present and only when the other vital organs are perfused, the perfusion of the skin will recover.

In four of the six experimental tests, the delay of increase in mitoPO$_2$ despite systemic reperfusion suggests irreversible damage to tissue perfusion, tissue oxygenation, or oxygen transport to the mitochondria. In these four tests, after the initial spike of high mitoPO$_2$ following ECPR initiation, no continuously high mitoPO$_2$ values were measured until the end of the experiment. In the two tests with recovery of the skin mitoPO$_2$ values, recovery of the tissue perfusion, tissue oxygenation, and oxygen transport to the mitochondria takes place. When high mitoPO$_2$ values were measured after the initial spike, the values remained high. The inadequacy of tissue oxygenation and long ischemic period could eventually lead to a microcirculatory shut down. A global shut down in cases of ischemia was already reported before. [20] After an ischemic episode, the microcirculation respiration can recover to a certain extent, depending on the duration of ischemia and level of reperfusion. [20] Ruggieri et al. [21] stated that, after severe ischemia some muscle cells in the heart can be irreversibly damaged and demarcation will occur, while the incompletely effected tissue can recover partly. The difference in mitoPO$_2$ course in the six experimental tests we performed could be explained by irreversible vs. incomplete effected tissue. We hypothesize that the quicker mitoPO$_2$ rises could be explained by less ischaemic cellular damage which could cause sooner reactivation of the mitochondrial function and therefore less overall ischaemic/reperfusion damage.

MitoPO$_2$ can be interpreted as determinant of the microcirculatory function. In order to regain oxygen levels into the mitochondria after cardiac arrest, tissue perfusion and tissue oxygenation have to be present. This tissue perfusion and oxygenation are largely influenced by an intact microcirculation. In case mitoPO$_2$ is detected, it can be expected that microcirculation has at least partly been recovered. Bodmer et al. [22] performed a study measuring the microcirculation and mitoPO$_2$ in the liver simultaneously. They found only a small difference of PO$_2$ in the microcirculation and mitoPO$_2$. Mik et al. [9] recently stated that average mitoPO$_2$ appears to be close to microvascular PO$_2$. MitoPO$_2$ measured by PpIX delayed fluorescence provides an estimation of microvascular PO$_2$ and therefore an it can be interpreted as determinant of the microcirculatory function.

The added value of monitoring microcirculatory function could be relevant in ECPR procedures, as the correlation between the mitoPO$_2$ and MAP is not consistently present in this study. In contrast to the abovementioned delay in recovery of tissue oxygenation due to an impaired microcirculatory function, the macrocirculation (MAP and blood flow) was restored immediately upon initiation of ECPR. This discrepancy between mitoPO$_2$, as a determinant of microcirculatory function, and MAP, as a determinant of macrocirculation, shows the importance of monitoring this microcirculatory function. Yu et al.

[23] compared the microcirculation and macrocirculation and showed an inconsistent relation of microcirculation (i.e., brain and brachioradial muscle) and macrocirculation (i.e., MAP) in pigs with cardiac arrest. [23] Fritz et al. [24] performed ECPR in pigs, they found no differences in microcirculatory flow index at initiation and after 6 h of ECPR comparing the group treated with standard MAP to the group treated with high MAP. However, they did not directly investigate the relation between continuous microcirculatory function and MAP. In addition, two other studies compared microcirculation and macrocirculation in patients with cardiogenic shock treated with veno-arterial ECMO (VA-ECMO). [25, 26] Yeh et al. [26] showed no differences in early MAP for survivors and non-survivors, while early microcirculation was higher in survivors than in non-survivors. Chommeloux et al. [25] showed in successfully weaned patients despite normal MAP, normalization of microcirculatory values took 48 h after initiation of VA-ECMO. In order to apply personalized medicine and therefore a possible increase in the accuracy of treatment, monitoring of microcirculatory function should be the added to monitoring of macrocirculation.

In addition, the survival chance in pigs with continuously high mitoPO$_2$ is probably higher than in pigs without continuously high mitoPO$_2$. One of the two cases with continuously high mitoPO$_2$ survived this experiment. The other one died because of technical failure. In the experiments with pigs without continuously high mitoPO$_2$, none of them survived. No previous studies aimed on the course of mitoPO$_2$ measurements in ECPR in relation to survival outcome. However, Fries et al. [17] found less increase in microcirculation (i.e., capillary flow) in animals that failed resuscitation in a model with chest compressions. Furthermore, within 5 min of ROSC, microcirculation returned only within 20% of baseline values. [17] This could point to the possible additional value of monitoring microcirculatory function during CPR, during ECPR, and after ROSC.

This study has several limitations. First, our sample size is small and of the experimental measurements only one pig survived. Therefore, we could not perform statistical tests to identify the correlation of the course of mitoPO$_2$ and survival or favorable neurological survival. Possible hypotheses for the low successful weaning numbers in this studies are described in the Supplementary Appendix B. Second, because of the preparation time of the ALA crème, mitoPO$_2$ measurements cannot be used during cardiac arrest and within the first hours after ECPR initiation in humans. In order to test our hypotheses and get more understanding of the pathophysiology, future experimental research should aim at the correlation of the course of mitoPO$_2$ and survival. Also, the course of mitoPO$_2$ comparing conventional CPR with ROSC and ECPR cases could extend the existing knowledge. Another topic which needs to be investigated in future research is if, in humans treated with ECPR, monitoring the microcirculatory function is a more accurate target than monitoring the macrocirculation in order to apply a more individually based treatment. If a method is found to shorten the time needed for ALA-

induced PpIX enhancement within cells (e.g., with intravenous administration), mitoPO_2 measurements during ECPR could be also performed in humans.

CONCLUSION

This experimental pilot study shows that continuous measurements of skin mitoPO_2 in pigs treated with ECPR are feasible. The delay in initial mitoPO_2 and discrepancy of mitoPO_2 and MAP in our small sample study could point to the possible value of additional measurements besides MAP to monitor the quality of tissue perfusion during cardiac arrest and ECPR.

REFERENCES

1. Martinell L, Nielsen N, Herlitz J, Karlsson T, Horn J, Wise MP, et al. Early predictors of poor outcome after out-of-hospital cardiac arrest. Crit Care. 2017;21:96.
2. Adnet F, Triba MN, Borron SW, Lapostolle F, Hubert H, Gueugniaud PY, et al. Cardiopulmonary resuscitation duration and survival in out-of-hospital cardiac arrest patients. Resuscitation. 2017;111:74-81.
3. Holmberg MJ, Geri G, Wiberg S, Guerguerian AM, Donnino MW, Nolan JP, et al. Extracorporeal cardiopulmonary resuscitation for cardiac arrest: A systematic review. Resuscitation. 2018;131:91-100.
4. Gvozdjáková A. Mitochondrial Medicine. Mitochondrial Medicine; Mitochondrial Metabolism, Diseases, Diagnosis and Therapy: Springer Science + Bussiness Media B.V.; 2008. p. 1-17.
5. Skulachev VP. Mitochondrial physiology and pathology; concepts of programmed death of organelles, cells and organisms. Mol Aspects Med. 1999;20:139-84.
6. Harms FA, de Boon WM, Balestra GM, Bodmer SI, Johannes T, Stolker RJ, et al. Oxygen-dependent delayed fluorescence measured in skin after topical application of 5-aminolevulinic acid. J Biophotonics. 2011;4:731-9.
7. Mik EG, Stap J, Sinaasappel M, Beek JF, Aten JA, van Leeuwen TG, et al. Mitochondrial PO2 measured by delayed fluorescence of endogenous protoporphyrin IX. Nat Methods. 2006;3:939-45.
8. Harms FA, Voorbeijtel WJ, Bodmer SI, Raat NJ, Mik EG. Cutaneous respirometry by dynamic measurement of mitochondrial oxygen tension for monitoring mitochondrial function in vivo. Mitochondrion. 2013;13:507-14.
9. Mik EG, Balestra GM, Harms FA. Monitoring mitochondrial PO2: the next step. Curr Opin Crit Care. 2020;26:289-95.
10. Ubbink R, Bettink MAW, Janse R, Harms FA, Johannes T, Munker FM, et al. A monitor for Cellular Oxygen METabolism (COMET): monitoring tissue oxygenation at the mitochondrial level. J Clin Monit Comput. 2017;31:1143-50.
11. Harms FA, Bodmer SI, Raat NJ, Stolker RJ, Mik EG. Validation of the protoporphyrin IX-triplet state lifetime technique for mitochondrial oxygen measurements in the skin. Opt Lett. 2012;37:2625-7.
12. Costerus SA, Bettink MW, Tibboel D, de Graaff JC, Mik EG. Mitochondrial Oxygen Monitoring During Surgical Repair of Congenital Diaphragmatic Hernia or Esophageal Atresia: A Feasibility Study. Front Pediatr. 2020;8:532.
13. Animals NRCUCftUotGftCaUoL. Guide for the Care and Use of Laboratory Animals. National Academies Press (US). 2011;8th ed. Washington (DC).
14. Forbess JM, Ibla JC, Lidov HG, Cioffi MA, Hiramatsu T, Laussen P, et al. University of Wisconsin cerebroplegia in a piglet survival model of circulatory arrest. Ann Thorac Surg. 1995;60:S494-500.
15. Taunyane IC, Benk C, Beyersdorf F, Foerster K, Cristina Schmitz H, Wittmann K, et al. Preserved brain morphology after controlled automated reperfusion of the whole body following normothermic circulatory arrest time of up to 20 minutes. Eur J Cardiothorac Surg. 2016;50:1025-34.
16. Gough CJR, Nolan JP. The role of adrenaline in cardiopulmonary resuscitation. Crit Care. 2018;22:139.
17. Fries M, Weil MH, Chang YT, Castillo C, Tang W. Microcirculation during cardiac arrest and resuscitation. Crit Care Med. 2006;34:S454-7.
18. McDonald JL. Systolic and mean arterial pressures during manual and mechanical CPR in humans. Ann Emerg Med. 1982;11:292-5.

19. Dunser MW, Takala J, Brunauer A, Bakker J. Re-thinking resuscitation: leaving blood pressure cosmetics behind and moving forward to permissive hypotension and a tissue perfusion-based approach. Crit Care. 2013;17:326.
20. Chun K, Zhang J, Biewer J, Ferguson D, Clemens MG. Microcirculatory failure determines lethal hepatocyte injury in ischemic/reperfused rat livers. Shock. 1994;1:3-9.
21. Ruggieri AJ, Levy RJ, Deutschman CS. Mitochondrial dysfunction and resuscitation in sepsis. Crit Care Clin. 2010;26:567-75, x-xi.
22. Bodmer SI, Balestra GM, Harms FA, Johannes T, Raat NJ, Stolker RJ, et al. Microvascular and mitochondrial PO(2) simultaneously measured by oxygen-dependent delayed luminescence. J Biophotonics. 2012;5:140-51.
23. Yu J, Ramadeen A, Tsui AK, Hu X, Zou L, Wilson DF, et al. Quantitative assessment of brain microvascular and tissue oxygenation during cardiac arrest and resuscitation in pigs. Anaesthesia. 2013;68:723-35.
24. Fritz C, Kimmoun A, Vanhuyse F, Trifan BF, Orlowski S, Falanga A, et al. High Versus Low Blood-Pressure Target in Experimental Ischemic Prolonged Cardiac Arrest Treated with Extra Corporeal Life Support. Shock. 2017;47:759-64.
25. Chommeloux J, Montero S, Franchineau G, Brechot N, Hekimian G, Lebreton G, et al. Microcirculation Evolution in Patients on Venoarterial Extracorporeal Membrane Oxygenation for Refractory Cardiogenic Shock. Crit Care Med. 2020;48:e9-e17.
26. Yeh YC, Lee CT, Wang CH, Tu YK, Lai CH, Wang YC, et al. Investigation of microcirculation in patients with venoarterial extracorporeal membrane oxygenation life support. Crit Care. 2018;22:200.

Chapter 7

Initial arterial pCO_2 and its course in the first hours of extracorporeal cardiopulmonary resuscitation show no association with recovery of consciousness in humans: A single-centre retrospective study

Loes Mandigers, Corstiaan A. den Uil, Jeroen J.H. Bunge, Diederik Gommers, Dinis dos Reis Miranda

Membranes 2021, 11(3), 208; doi: 11030208

ABSTRACT

Background Cardiac arrest is a severe condition with high mortality rates, especially in the case of prolonged low-flow durations resulting in severe ischaemia and reperfusion injury. Changes in partial carbon dioxide concentration (pCO_2) may aggravate this injury. Extracorporeal cardiopulmonary resuscitation (ECPR) shortens the low-flow duration and enables close regulation of pCO_2. We examined whether pCO_2 is associated with recovery of consciousness.

Methods We retrospectively analysed ECPR patients ≥ 16 years old treated between 2010 and 2019. We evaluated initial arterial pCO_2 and the course of pCO_2 ≤ 6 h after initiation of ECPR. The primary outcome was the rate of recovery of consciousness, defined as Glasgow coma scale motor score of six.

Results Out of 99 ECPR patients, 84 patients were eligible for this study. The mean age was 47 years, 63% were male, 93% had a witnessed arrest, 45% had an out-of-hospital cardiac arrest, and 38% had a recovery of consciousness. Neither initial pCO_2 (Odds Ratio (OR) 0.93, 95% confidence interval 95% (CI) 0.78–1.08) nor maximum decrease of pCO_2 (OR 1.03, 95% CI 0.95–1.13) was associated with the recovery of consciousness.

Conclusion: Initial arterial pCO_2 and the course of pCO_2 in the first six hours after initiation of ECPR were not associated with the recovery of consciousness.

Keywords: cardiac arrest; heart arrest; extracorporeal cardiopulmonary resuscitation; extracorporeal membrane oxygenation; carbon dioxide; outcome

INTRODUCTION

Survival and favourable neurological survival after cardiac arrest are highly influenced by low-flow duration and the associated severity of ischaemia and reperfusion injury [1]. This ischaemia and reperfusion injury is influenced by the level and course of partial oxygen pressure (pO_2) and partial carbon dioxide pressure (pCO_2) during and after cardiopulmonary resuscitation (CPR) [2]. During CPR, hypoxemia causes neuron ischaemia and cell death whereas hypercapnia causes cerebrovascular vasodilatation, which may raise intracranial pressure [2]. After regaining circulation, pO_2 and pCO_2 will change immediately, which can contribute to reperfusion injury. Especially in the case of hyperoxemia, oxygen-free radicals will be produced causing intracellular oxidation. If hypocapnia occurs, this will result in cerebrovascular vasoconstriction, causing a decreased CBF [2]. Clinically, the importance of regulating pO_2 during and after conventional CPR has already been proven [3-5]. However, research in pCO_2 values is more limited and the results vary a lot [3-7].

In an attempt to limit ischaemia and reperfusion injury, extracorporeal cardiopulmonary resuscitation (ECPR) can be used to restore circulation to vital organs as soon as possible. The use of this ECPR enables very fast oxygenation and decarboxylation. However, it is not clear whether these changes in pO_2 and pCO_2 should occur rapidly. In patients treated with ECPR, hypoxemia as well as hyperoxemia are associated with lower survival rates [8,9]. The best neurological survival outcomes are seen in patients with normoxia [8]. Despite the possible effects of pCO_2 in ischaemia and reperfusion, limited studies have been performed on the course of pCO_2 during and after ECPR. A recent study showed that a large decrease of pCO_2 after initiation of extracorporeal membrane oxygenation (ECMO) for respiratory failure is associated with neurological complications [10].

We hypothesise that in ECPR, a rapid decrease in pCO_2 could simulate the occurrence of hypocapnia, leading to cerebral vasoconstriction, which could have a negative impact on neurological outcomes. Therefore, the aim of this study was to investigate the association between pCO_2 in the first hours after initiation of ECPR and the recovery of consciousness.

MATERIALS AND METHODS

We performed a retrospective study at the Erasmus University Medical Centre in Rotterdam, the Netherlands. This hospital has a local database in which all adult patients treated at the emergency department and/or patients of ≥16 years old admitted to the intensive care unit (ICU) for adults, treated with ECMO are registered. The study

was conducted in accordance with the Declaration of Helsinki, and the Medical Ethics Committee of the Erasmus University Medical Centre reviewed and approved the study protocol (number MEC-2019-0681). The need for informed consent was waived.

Patients

All patients treated with ECMO who received ECPR in the period 1 January 2010 until 1 January 2020 were selected. After initiation of ECPR, at least three arterial blood gas analyses within the first 6 h had to be known. We excluded all patients with return of spontaneous circulation (ROSC) before ECPR initiation. In our hospital, we consider ECPR in both out of hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) patients when the following criteria are met: age ≤ 70 years, witnessed cardiac arrest (last seen < 5 min), good quality of basic life support (BLS) or advanced life support (ALS) leading to an end-tidal carbon dioxide >1.33 kPa, maximum no-flow time of 5 min, a low flow duration of <60 min at the start of ECPR placement, no known terminal illnesses, and no impairment of daily living activities.

ECPR Procedure

ECPR placement was performed by an interventional cardiologist, cardiothoracic surgeon or intensivist, depending on the location where the patient resided. This procedure is mostly performed percutaneously and ultrasound-guided. In the case this is not successful, or if it is performed in the operation room, it is performed surgically. The cannulas are placed in the femoral artery and femoral vein. Every patient receives an antegrade cannula in order to perfuse the leg distally from the cannula placement. Cannulation was started at a minimum CPR duration of 20 min. The decision to contact the ECPR team was made by the attending intensivist. For OHCA patients, we first started with ECPR procedures in patients with massive pulmonary embolism as the cause of arrest. Starting from 1 February 2019, every OHCA patient could be eligible for ECPR.

Measured Variables

We extracted the following variables: patient characteristics (sex, age, and body mass index (BMI)); clinical characteristics (Acute Physiology and Chronic Health Evaluation (APACHE) IV-score, witnessed the arrest, OHCA/IHCA, BLS, direct life support (i.e., BLS or ALS); no-flow duration, low-flow duration, mechanical compression device, primary cardiac rhythm, location of arrest, cause of arrest, laboratory results, and complications); and outcomes (primary outcome: recovery of consciousness and secondary outcomes: ECMO survival, ICU-survival, hospital survival, and cause of death). All known pre-ECMO data were reported according to the Utstein criteria [11].

Statistical Analysis

The distribution of the variables was tested using the Shapiro–Wilk test. Normally distributed continuous variables were reported as mean and standard deviation (SD), and categorical variables as numbers and percentages (%). Non-normally distributed continuous variables were reported as median and interquartile ranges (IQR). To study statistical differences of continuous variables, we used the unpaired T-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. For the categorical variables, we used the Chi2 test or the Fisher's exact test depending on the numbers in each cell.

To examine the possible effect of pCO_2 on our primary outcome, we performed a binary logistic regression analysis. We included the following pCO_2 values: initial pCO_2 value after initiation of EPCR (defined as the first arterial pCO_2 after starting ECMO flow or the last pCO_2 within five minutes before starting ECMO flow), course of pCO_2 (defined as the slope between the first and last pCO_2 measurement within 6 h), and the interaction between the initial pCO_2 and the course of pCO_2. Next, we performed a binary logistic regression analysis including the initial pCO_2 value after initiation of EPCR, the maximum decrease of pCO_2 (defined as the maximum percentage of decrease per hour between two measurements within 6 h after initiation of ECPR), and the interaction between the initial pCO_2 and the maximum decrease of pCO_2. As sensitivity analyses, we performed binary logistic regression analysis for sustained regain of consciousness at hospital discharge and expected a neurologically favourable outcome at any time after hospital discharge. This expected favourable neurological outcome was determined by reviewing patient charts. A p-value < 0.05 was defined as statistically significant and the analyses were performed in R studio, version 3.6.0.

RESULTS

In our ECMO database, 99 patients underwent ECPR. We excluded patients with two or less arterial blood gas measurements after initiation of ECPR (n = 11), and we excluded patients with ROSC before ECPR initiation (n = 4). A total of 84 patients were included in this study, of which 32 (38%) had a recovery of consciousness at the ICU. Patient characteristics, clinical characteristics, and outcomes are shown in Table 1.

Clinical Characteristics

The mean age of the patients was 47 years (SD 16), and the majority of the patients were male (n = 53, 63%). Almost half of the patients had an OHCA (n = 38, 45%), and in 78 patients (93%) the arrest was witnessed. The median low-flow duration was 51 min (IQR 37–80). This duration did not significantly differ between patients who recovered

Table 1 | Characteristics of extracorporeal cardiopulmonary resuscitation (ECPR) patients for patients who did and did not experience a recovery of consciousness.

	Total	Recovery of consciousness (N= 32)	No recovery of consciousness (N= 56)	p-value
Patient number (%)	84	32 (38.1)	52 (61.9)	
Patient characteristics				
Age in years (SD)	46.9 (15.6)	47.1 (15.5)	46.7 (15.7)	0.91
Sex; Male (%)	53 (63.1)	19 (59.4)	34 (65.4)	0.75
BMI (IQR)	26.3 (24.6; 29.8)	26.5 (25.2; 30.1)	25.8 (24.5; 29.4)	0.40
Clinical characteristics				
Apache IV-score (SD) (Missing N= 36)	112 (31)	110 (36)	113 (27)	0.74
Witnessed arrest (%)	78 (92.9)	31 (96.9)	47 (90.4)	0.40
OHCA (%)	38 (45.2)	13 (40.6)	25 (48.1)	0.66
BLS (%)	37 (44.0)	15 (46.9)	22 (42.3)	0.85
Direct life support (%)	79 (94.0)	30 (93.8)	49 (94.2)	1.00
No-flow in minutes (IQR)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.25
Total low-flow duration in minutes (IQR) **(**Missing N=3)	51.0 (37.0; 80.0)	45.0 (30.0; 76.5)	58.0 (40.0; 84.0)	0.24
Mechanical compression device, e.g. LUCAS (%)	27 (32.1)	6 (18.8)	21 (41.2)	0.06
Primary cardiac rhythm				
Shockable (%)	26 (31.0)	11 (34.4)	15 (29.4)	0.82
Ventricular fibrillation (%)	23 (27.4)	9 (28.0)	14 (28.1)	1.00
Ventricular tachycardia (%)	3 (3.6)	2 (6.3)	1 (2.0)	0.56
Non-shockable (%)	57 (68.7)	21 (65.6)	36 (70.6)	0.82
Pulseless electrical activity (%)	47 (56.0)	20 (62.5)	27 (54.0)	0.60
Asystole (%)	9 (10.7)	1 (3.1)	8 (16.0)	0.08
Location of arrest				
Home (%)	23 (27.4)	8 (25.0)	15 (28.8)	0.90
Public (%)	13 (15.5)	5 (15.6)	8 (15.4)	1.00
ICU (%)	24 (28.6)	9 (28.1)	16 (30.8)	0.99
Ward (%)	10 (11.9)	3 (9.4)	7 (13.5)	0.73
Emergency department (%)	4 (4.8)	1 (3.1)	3 (5.8)	1.00
Operation room (%)	4 (4.8)	3 (9.4)	1 (1.9)	0.15
Catherisation laboratory (%)	3 (3.6)	3 (9.4)	0 (0.0)	0.14
Other (%)	1 (1.2)	0 (0.0)	1 (1.9)	1.00
Cause of arrest				
Acute coronary syndrome (%)	25 (29.8)	12 (37.5)	13 (25.0)	0.33

Table 1 | Characteristics of extracorporeal cardiopulmonary resuscitation (ECPR) patients for patients who did and did not experience a recovery of consciousness. (*continued*)

	Total	Recovery of consciousness (N= 32)	No recovery of consciousness (N= 56)	p-value
Pulmonary embolism (%)	30 (35.7)	11 (34.4)	19 (36.5)	1.00
Tamponade (%)	3 (3.6)	2 (6.3)	1 (1.9)	0.55
Hypothermia/drowning (%)	5 (6.0)	1 (3.1)	4 (7.8)	0.64
Post cardiac surgery (%)	2 (2.4)	0 (0.0)	2 (3.8)	0.52
Cardiac infection (%)	5 (6.0)	2 (6.3)	3 (5.8)	1.00
Heart failure (%)	3 (3.6)	2 (6.3)	1 (1.9)	0.55
Hypoxemia (%)	2 (2.4)	0 (0.0)	2 (3.8)	0.52
Sepsis (%)	2 (2.4)	1 (3.1)	1 (1.9)	1.00
Other (%)	5 (6.0)	0 (0.0)	5 (9.6)	0.15
Unknown (%)	2 (2.4)	1 (3.1)	1 (1.9)	1.00
Complications				
Bleeding (%)	56 (66.7)	24 (75)	32 (61.5)	0.30
Limb ischaemia (%)	5 (6.0)	2 (6.3)	3 (5.8)	1.00
Cerebrovascular accident (%)	6 (7.1)	4 (12.5)	2 (3.8)	
Cerebral bleeding (%)	5 (6.0)	3 (9.4)	2 (3.8)	0.36
Cerebral infarction (%)	1 (1.2)	1 (3.1)	0 (0.0)	0.38
Infection (%)	28 (33.3)	16 (50.0)	12 (25.0)	**0.04**
Acute kidney injury (%)	43 (51.2)	21 (65.6)	23 (44.2)	0.09
CRRT (%)	15 (17.9)	6 (18.8)	9 (17.3)	1.00
Tamponade (%)	6 (7.1)	2 (6.3)	4 (7.7)	1.00
Abdominal compartment syndrome (%)	4 (4.8)	1 (3.1)	3 (5.8)	1.00
Laboratory results				
Initial pCO2 in kpa (IQR)	7.3 (5.7; 9.9)	7.1 (5.3; 8.9)	7.7 (6.0; 9.9)	0.30
Course of pCO2 in %/h (IQR)	-5.22 (-8.69; -1.99)	-4.09 (-8.38; -1.30)	-6.28 (-8.69; -2.08)	0.37
Maximum decrease pCO2 in %/hour (IQR)	0.67 (0.38; 1.06)	0.58 (0.24; 1.06)	0.72 (0.41; 0.82)	0.43
Maximum difference pCO2 in %/hour (IQR)	-0.52 (-0.87; 0.39)	-0.30 (-0.88; 0.08)	-0.59 (-0.86; 0.71)	0.76
Initial pO2 in kpa (IQR)	25.3 (10.8; 43.5)	17.4 (9.4; 42.5)	32.8 (11.5-47.1)	0.10
Course of pO2 in %/hour (IQR)	-6.29 (-11.65; 9.31)	-4.26 (-12.85; 12.53)	-7.15 (-11.30; 5.97)	0.90
Initial pH (IQR)	6.96 (6.80; 7.08)	7.07 (6.84; 7.21)	6.90 (6.79; 7.00)	**<0.01**
Course of pH in %/hour (SD)	0.68 (0.53)	0.68 (0.48)	0.69 (0.57)	0.98
Initial lactate in mmol/L (SD)	13.7 (5.8)	12.5 (6.0)	14.5 (5.7)	0.14
Course of lactate in %/h (IQR)	-7.44 (-11.89; -1.33)	-10.38 (-12.98; -5.06)	-6.11 (-11.12; -5.48)	**<0.05**

Table 1 | Characteristics of extracorporeal cardiopulmonary resuscitation (ECPR) patients for patients who did and did not experience a recovery of consciousness. (*continued*)

	Total	Recovery of consciousness (N= 32)	No recovery of consciousness (N= 56)	p-value
Outcomes				
ECMO survival (%)	32 (38.1)	28 (87.5)	4 (7.7)	**<0.01**
ICU-survival (%)	25 (29.8)	24 (75.0)	1 (1.9)	**<0.01**
Hospital survival (%)	24 (28.6)	23 (71.9)	1 (1.9)	
Cause of death	N=59	N=9	N=50	
Brain death (%)	5 (8.5)	0 (0.0)	5 (10.0)	1.00
Diagnosis life incompatible (%)	41 (69.5)	7 (77.8)	34 (68.0)	0.85
Neurology (%)	23 (56.1)	4 (57.1)	19 (57.8)	
Neurology + other (%)	6 (14.6)	1 (14.3)	5 (15.2)	
Cardiac (%)	2 (4.9)	0 (0.0)	2 (5.9)	
Multi-organ disease (%)	3 (7.3)	1 (14.3)	3 (8.8)	
No treatment options (%)	4 (9.8)	1 (14.3)	3 (9.1)	
Other (%)	2 (4.9)	0 (0.0)	2 (5.9)	
Haemorrhagic shock (%)	2 (2.4)	0 (0.0)	2 (4.0)	1.00
Heart failure (%)	2 (2.4)	1 (11.1)	1 (2.0)	0.28
Multi-organ disease (%)	5 (8.5)	0 (0.0)	5 (10.0)	1.00
Persisting cardiac arrest (%)	2 (2.4)	0 (0.0)	2 (4.0)	1.00
Other (%)	2 (2.4)	1 (11.1)	1 (1.9)	0.15

ECPR: extracorporeal cardiopulmonary resuscitation, BMI: body mass index, OHCA: out of hospital cardiac arrest, BLS: basic life support, ICU: intensive care unit, CRRT: continuous renal replacement therapy, T0: initial time point, Tmax: maximum time value known within 6 hours after initiation, pCO2: partial carbon dioxide concentration, pO2: partial oxygen concentration

consciousness versus patients who did not recover consciousness. Most patients had a non-shockable primary cardiac rhythm (n = 57, 69%). We found no significant difference in the primary cardiac rhythm for patients with and without recovery of consciousness. The cause of arrest was primarily pulmonary embolism (36%) followed by acute coronary syndrome (30%).

Laboratory Results

Patients with the recovery of consciousness had higher median pH values (7.07, IQR 6.84–7.21) than patients without the recovery of consciousness (6.90, IQR 6.79–7.00, $p < 0.01$). No differences were seen in initial pO_2 values ($p = 0.10$) and initial lactate values ($p = 0.14$) for patients with the recovery of consciousness and patients without the recovery of consciousness. The decrease in lactate values from initiation of ECPR until

six hours after initiation of ECPR was significantly higher in patients with the recovery of consciousness (10.38%/h, IQR 12.98–5.06) than in patients without the recovery of consciousness (6.11%/h IQR 11.12–5.48, $p < 0.05$). No significant differences were found in changes of pH and pO_2 values from initiation of ECPR until six hours after initiation of ECPR.

Table 2 | Binary logistic regression analysis of ECPR patients regarding pCO_2 measurements and the recovery of consciousness.

	(a)	(b)	(c)	(d)	(e)
Initial pCO2	0.93 (0.78; 1.09)	0.97 (0.79; 1.20)	0.92 (0.65; 1.30)	0.94 (0.78; 1.12)	0.75 (0.52; 1.05)
Course of pCO2 in first 6 hours		1.03 (0.96; 1.13)	1.05 (0.92; 1.26)		
Interaction initial & course pCO2			0.99 (0.97; 1.02)		
Maximum decrease of pCO2 in first 6 hours				1.07 (0.48; 2.30)	0.14 (0.01; 2.07)
Interaction initial & maximum decrease pCO2					1.29 (0.93; 1.88)
N	83	83	83	80	80
Nagelkerke R2	0.03	0.04	0.04	0.10	0.13
AIC	113.82	115.22	117.06	111.36	111.02

The values are displayed as odds ratios with 95% confidence intervals (CI). T0: initial values, pCO2: partial carbon dioxide concentration.

Outcomes

In total, 32 patients (38%) could be weaned from the ECMO: 28 (33%) of these patients recovered consciousness. Twenty-five patients (30%) survived ICU admission, and 24 patients (29%) survived until hospital discharge. Of those, only one patient (2%) did not recover consciousness. This patient was transferred to another hospital with a Glasgow coma scale motor score of five. In most cases, the cause of death was neurologic (47%, of which 9% brain death and 39% other neurologic causes).

As shown in Table 2, the initial pCO_2 or pCO_2 courses were not associated with the recovery of consciousness. In Supplementary Material Figure S1, we included the courses of pCO_2 in the first six hours after initiation of ECPR for every individual patient. As a sensitivity analysis, we performed the binary logistic regression for patients who had a sustained recovery of consciousness at hospital discharge. These results are shown in Supplementary Material Table S1. Additionally, we determined an expected neurological favourable outcome based on patient charts (classified as cerebral performance category (CPC) score 1–2) at any time from hospital discharge, shown in Supplemen-

tary Material Table S2. We also performed the binary logistic regression based on this outcome. As shown in Supplementary Material Table S3, these sensitivity analyses, no significant differences were found.

DISCUSSION

In this study, we found that initial pCO_2 values and the course of pCO_2 after initiation of ECPR are not associated with the recovery of consciousness. We also found no significant difference for initial pO_2 values, course of pO_2 and pH, and initial lactate values. In patients with recovery of consciousness, we found a significantly higher initial pH and a significantly more rapid decrease of lactate than in patients without recovery of consciousness.

Contrary to our hypothesis, recovery of consciousness was not associated with a less rapid decrease of pCO_2 in the first hours after initiation of ECPR. Based on these findings, a rapid decrease of pCO_2 until normocapnia might not negatively influence cerebral perfusion. Some studies performed in patients treated with conventional CPR examined the effects of pCO_2 on survival. Wang et al. [5] evaluated the presence of hypercapnia and hypocapnia in the first 24 h after hospital arrival. They found increased hospital mortality in the case of any hypercapnia or for final hypocapnia [5]. Helmerhorst et al. [3] found only increased hospital mortality in the case of a single measurement of hypocapnia in the first 24 h in patients admitted to the ICU in the Netherlands. In contrast to these two studies, Vaahersalo et al. [7] found a positive association for the duration of hypercapnia within the first 24 h on good neurological outcome. However, these studies did not evaluate the effects of the course of pCO_2 on the outcome. Ebner et al. [6] did study this course of pCO_2 in cardiac arrest patients not treated with ECPR. Similar to our results, they have shown no significant association of maximum amplitude in pCO_2 with poor neurological outcome. Additionally, they also found no significant difference for an area under the curve analysis for the first four pCO_2 measurements as well as all pCO_2 measurements and neurological outcomes [6]. In a study by Bemtgen et al. [12], pCO_2 values were measured several times in the first 24 h after ECPR initiation. They found no significant difference in survival for patients with hypercapnia, hypocapnia, and normocapnia [12].

In addition to our primary outcome, we found three other results in the univariate analyses. First, we found a trend for lower initial pO_2 values in patients with recovery of consciousness than in patients without recovery of consciousness. This is in line with the recent study by Halter et al. [9] They have shown that ECPR patients with hyperoxemia had a higher odds ratio (OR) for mortality at day 28 (OR 1.89, 95% confidence interval (CI) 1.74–2.07) [9]. These findings suggest that the outcome may be improved by using

an oxygen blender with careful titration of the percentage of oxygen for membrane gas flow.

Second, in this study, patients with recovery of consciousness had a slightly higher initial pH than patients without recovery of consciousness. A comparable result was found by Bemtgen et al. [12], who have shown higher survival rates in patients with higher pH values during the first 24 h after initiation of ECPR. However, when compared with the study of Bartos et al. [13], it seems that pH values before ECPR initiation are not associated with survival with favourable neurological outcomes. Despite the possible positive association of higher pH and favourable outcomes, the differences are small (the difference of median pH between patients with and without recovery of consciousness was 0.17). Therefore, it is still not possible to determine at which pH a patient will or will not be eligible for ECPR.

Last, we found a higher lactate decrease in the first six hours after initiation of ECPR in patients who had recovery of consciousness than in patients without recovery of consciousness. This significant difference in lactate clearance is in line with the results found by Mizutani et al. [14]. They found a neurologically favourable survival rate (cerebral performance category 1–2) of 63.1% in patients with high lactate clearance and a neurologically favourable survival rate of 22.2% in patients with low lactate clearance after ECPR.

This study also had some limitations. First, the arterial blood gas sampling was not scheduled, so the measurements were performed by indication decided by the treating physicians. Therefore, the number of samples as well as the time between the samples was varying a lot and could have influenced the outcome of the study. In order to minimize this influence, we divided the samples into time frames. Second, the number of included patients was quite small. Due to this small sample, we were not able to perform a multivariable logistic regression analysis. There were no significant differences between the patient characteristics and cardiac arrest characteristics of the patients with and without recovery of consciousness. However, some of the cardiac arrest characteristics could have influenced the outcome. Third, we included a high rate of patients with non-cardiac causes of arrest. In order to determine if the initial pCO_2 or low-flow duration in patients with cardiac versus non-cardiac causes of arrest influenced the outcome, we studied these variables and did not find a statistically significant difference. Fourth, in this study we found high rates of BLS in OHCA patients, short no-flow durations, and limited low-flow durations. In the Netherlands, bystander CPR rates, population educated to perform bystander CPR, and use of an automatic external defibrillator (AED) is high and rising every year [15,16]. In our ECPR program, we select patients with an assumed high chance of favourable outcomes (i.e., patients with witnessed arrest, short no-flow times, high quality of CPR, and low-flow durations of <60 min). The selection of ECPR patients, high CPR education, and AED use probably explains the high rates of direct start

of BLS and associated short no-flow durations in this study. Last, due to the hypothesis, it could be that the physicians have adjusted the ECPR settings in order to prevent a rapid decrease in pCO_2. This could result in lower maximum decreases. Therefore, it would be advisable to repeat this study in another patient sample.

We did not find an association between the course of pCO_2 in the first hours after initiation of ECPR and the recovery of consciousness. Future studies should focus on performing analyses of arterial blood gas values after initiation of ECPR in order to determine the most optimal ECMO settings for neurological favourable outcomes. These studies should be performed in larger samples and with blood gas analyses at set time points.

CONCLUSIONS

Initial arterial pCO_2 and the course of pCO_2 in the first six hours after initiation of ECPR were not associated with the recovery of consciousness.

REFERENCES

1. Rea, T.D.; Cook, A.J.; Hallstrom, A. CPR during ischemia and reperfusion: A model for survival benefits. Resuscitation 2008, 77, 6–9. [Google Scholar] [CrossRef] [PubMed]
2. Sekhon, M.S.; Ainslie, P.N.; Griesdale, D.E. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: A "two-hit" model. Crit. Care 2017, 21, 1–10. [Google Scholar] [CrossRef] [PubMed]
3. Helmerhorst, H.J.; Roos-Blom, M.J.; van Westerloo, D.J.; Abu-Hanna, A.; de Keizer, N.F.; de Jonge, E. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. Crit. Care 2015, 19, 348. [Google Scholar] [CrossRef] [PubMed]
4. Roberts, B.W.; Kilgannon, J.H.; Hunter, B.R.; Puskarich, M.A.; Pierce, L.; Donnino, M.; Leary, M.; Kline, J.A.; Jones, A.E.; Shapiro, N.I.; et al. Association between Early Hyperoxia Exposure after Resuscitation from Cardiac Arrest and Neurological Disability: Prospective Multicenter Protocol-Directed Cohort Study. Circulation 2018, 137, 2114–2124. [Google Scholar] [CrossRef] [PubMed]
5. Wang, H.E.; Prince, D.K.; Drennan, I.R.; Grunau, B.; Carlbom, D.J.; Johnson, N.; Hansen, M.; Elmer, J.; Christenson, J.; Kudenchuk, P.; et al. Post-resuscitation arterial oxygen and carbon dioxide and outcomes after out-of-hospital cardiac arrest. Resuscitation 2017, 120, 113–118. [Google Scholar] [CrossRef] [PubMed]
6. Ebner, F.; Harmon, M.B.; Aneman, A.; Cronberg, T.; Friberg, H.; Hassager, C.; Juffermans, N.; Kjærgaard, J.; Kuiper, M.; Mattsson, N.; et al. Carbon dioxide dynamics in relation to neurological outcome in resuscitated out-of-hospital cardiac arrest patients: An exploratory Target Temperature Management Trial substudy. Crit. Care 2018, 22, 196. [Google Scholar] [CrossRef] [PubMed]
7. Vaahersalo, J.; Bendel, S.; Reinikainen, M.; Kurola, J.; Tiainen, M.; Raj, R.; Pettilä, V.; Varpula, T.; Skrifvars, M.B.; FINNRESUSCI Study Group. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: Associations with long-term neurologic outcome. Crit. Care Med. 2014, 42, 1463–1470. [Google Scholar] [CrossRef] [PubMed]
8. Chang, W.T.; Wang, C.H.; Lai, C.H.; Yu, H.Y.; Chou, N.K.; Wang, C.H.; Huang, S.-C.; Tsai, P.R.; Chou, F.-J.; Tsai, M.-S.; et al. Optimal Arterial Blood Oxygen Tension in the Early Postresuscitation Phase of Extracorporeal Cardiopulmonary Resuscitation: A 15-Year Retrospective Observational Study. Crit. Care Med. 2019, 47, 1549–1556. [Google Scholar] [CrossRef] [PubMed]
9. Halter, M.; Jouffroy, R.; Saade, A.; Philippe, P.; Carli, P.; Vivien, B. Association between hyperoxemia and mortality in patients treated by eCPR after out-of-hospital cardiac arrest. Am. J. Emerg. Med. 2020, 38, 900–905. [Google Scholar] [CrossRef] [PubMed]
10. Cavayas, Y.A.; Munshi, L.; Del Sorbo, L.; Fan, E. The Early Change in PaCO2 after Extracorporeal Membrane Oxygenation Initiation Is Associated with Neurological Complications. Am. J. Respir. Crit. Care Med. 2020, 201, 1525–1535. [Google Scholar] [CrossRef] [PubMed]
11. Nolan, J.P.; Berg, R.A.; Andersen, L.W.; Bhanji, F.; Chan, P.S.; Donnino, M.W.; Lim, S.H.; Ma, M.H.-M.; Nadkarni, V.M.; Starks, M.A.; et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Template for In-Hospital Cardiac Arrest: A Consensus Report From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia). Circulation 2019, 140, e746–e757. [Google Scholar] [PubMed]

12. Bemtgen, X.; Schroth, F.; Wengenmayer, T.; Biever, P.M.; Duerschmied, D.; Benk, C.; Bode, C.; Staudacher, D.L. How to treat combined respiratory and metabolic acidosis after extracorporeal cardiopulmonary resuscitation? Crit. Care 2019, 23, 183. [Google Scholar] [CrossRef] [PubMed]
13. Bartos, J.A.; Grunau, B.; Carlson, C.; Duval, S.; Ripeckyj, A.; Kalra, R.; Raveendran, G.; John, R.; Conterato, M.; Frascone, R.J.; et al. Improved Survival with Extracorporeal Cardiopulmonary Resuscitation Despite Progressive Metabolic Derangement Associated with Prolonged Resuscitation. Circulation 2020, 141, 877–886. [Google Scholar] [CrossRef] [PubMed]
14. Mizutani, T.; Umemoto, N.; Taniguchi, T.; Ishii, H.; Hiramatsu, Y.; Arata, K.; Takuya, H.; Inoue, S.; Sugiura, T.; Asai, T.; et al. The lactate clearance calculated using serum lactate level 6 h after is an important prognostic predictor after extracorporeal cardiopulmonary resuscitation: A single-center retrospective observational study. J. Intensive Care 2018, 6, 33. [Google Scholar] [CrossRef] [PubMed]
15. Blom, M.T.; Beesems, S.G.; Homma, P.C.M.; Zijlstra, J.A.; Hulleman, M.; Van Hoeijen, D.A.; Bardai, A.; Tijssen, J.G.P.; Tan, H.L.; Koster, R.W. Improved Survival After Out-of-Hospital Cardiac Arrest and Use of Automated External Defibrillators. Circulation 2014, 130, 1868–1875. [Google Scholar] [CrossRef] [PubMed]
16. Hartstichting. Jaarverslag 2019. Werken aan een Hartgezonde Samenleving. Available online: https://magazines.hartstichting.nl/jaarverslag2019/cover/?_ga=2.261012493.1236433838.1615061661-1639466317.1605858018 (accessed on 5 March 2021).

SUPPLEMENTARY MATERIALS

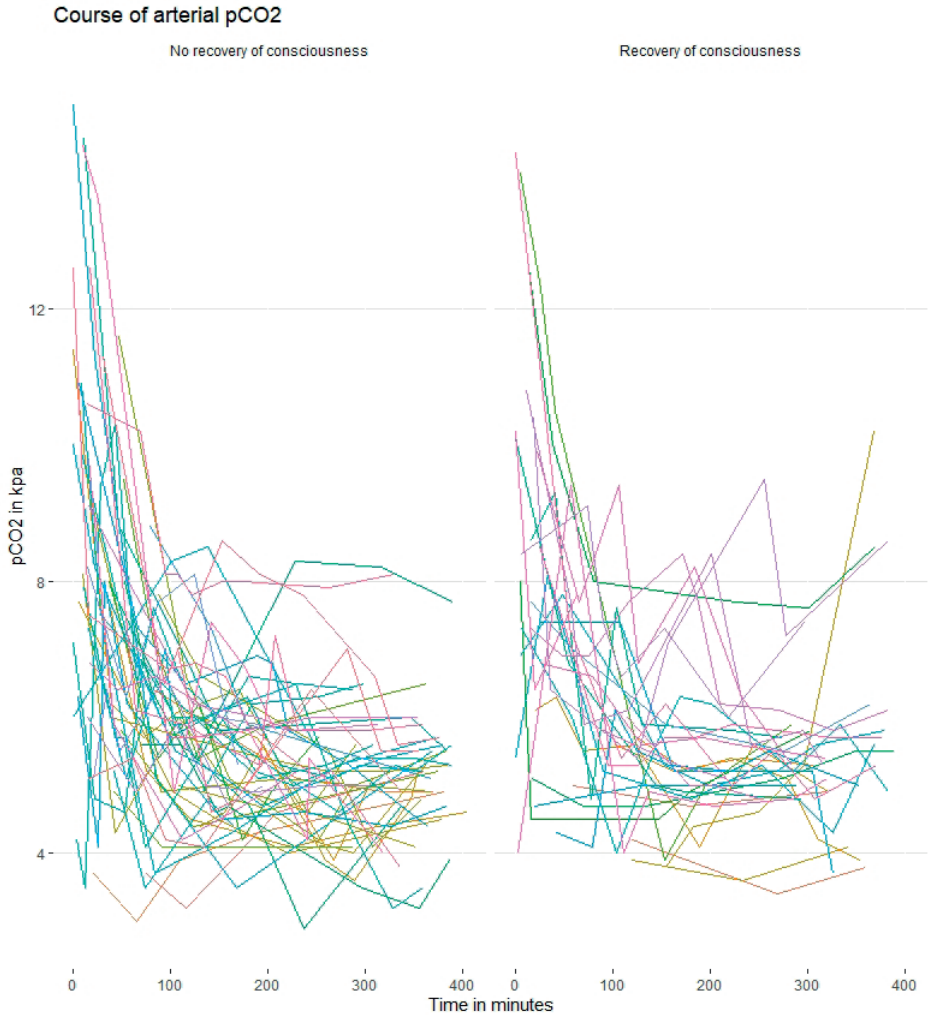


Figure A | Course of arterial pCO_2 in patients with and without recovery of consciousness
Course of the arterial pCO_2 in the first six hours after initiation of extracorporeal cardiopulmonary resuscitation of every individual patient divided in patients with and without recovery of consciousness. Partial carbon dioxide concentration (pCO_2).

Table A | Binary logistic regression analysis of ECPR patients regarding pCO_2 measurements and persisting recovery of consciousness (GCS 6 at hospital discharge).

	(a)	(b)	(c)	(d)	(e)
Initial pCO_2	0.97 (0.81-1.14)	1.04 (0.83; 1.29)	1.11 (0.76; 1.67)	0.99 (0.81; 1.20)	0.87 (0.60; 1.23)
Course of pCO_2 in first 6 hours		68.52 (0.04; 1,434,915)	3.98 (0.00000057; 73,391,710)		
Interaction initial & course pCO_2			1.92 (0.13; 57.72)		
Maximum decrease of pCO_2 in first 6 hours				1.13 (0.47; 2.53)	0.34 (0.02; 5.73)
Interaction initial & maximum decrease pCO_2					1.16 (0.83; 1.67)
N	83	83	83	80	80
Nagelkerke R2	0.01	0.04	0.04	0.11	0.12
AIC	115.20	102.56	104.40	98.00	99.24

The values are displayed as odds ratios with 95% confidence intervals. T0: initial values, pCO_2: partial carbon dioxide concentration.

Table B | CPC scores and expected CPC scores at any time after hospital discharge

Expected CPC score of 1-2	N =
CPC 1-2 at CPC questionnaire	6
EQ-5D-5L questionnaire: independent functioning	6
Functioning in home environment	6
Working again	1
Expected CPC score 3 or unknown outcome	
Unknown; transferred to other hospital with M6 score	3
CPC 3 at CPC questionnaire (both living at home, one cannot function independently for 24 hours a day and 1 needs care for physical problems)	2

In some patients CPC score was tested by a questionnaire (Mak et al, 20..), in other patients the CPC score was estimated based on information reported in the patient files. CPC = cerebral performance category

Table C | Binary logistic regression analysis of ECPR patients regarding pCO_2 measurements and expected favourable neurological outcome.

	(a)	**(b)**	**(c)**	**(d)**	**(e)**
Initial pCO_2	0.98 (0.81-1.18)	1.14 (0.89; 1.47)	1.47 (0.94; 2.41)	1.03 (0.83; 1.26)	0.89 (0.60; 1.30)
Course of pCO_2 in first 6 hours		4169.16 (0.80; $3.79*10^9$)	0.05 ($2.78*10^{-10}$; $8.54*10^7$)		
Interaction initial & course pCO_2			13.15 (0.34; 1055.56)		
Maximum decrease of pCO_2 in first 6 hours				1.08 (0.83; 2.54)	0.27 (0.01; 6.08)
Interaction initial & maximum decrease pCO_2					1.18 (0.82; 1.74)
N	83	83	83	80	80
Nagelkerke R2	<0.01	0.07	0.11	0.13	0.15
AIC	90.78	89.15	89.37	85.92	87.09

The values are displayed as odds ratios with 95% confidence intervals. T0: initial values, pCO_2: partial carbon dioxide concentration.

Chapter 8

Survival and neurological outcome with extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest caused by massive pulmonary embolism: A two center observational study

Loes Mandigers, Erik Scholten, Wim J.R. Rietdijk, Corstiaan A. den Uil, Robert J. van Thiel, Sander Rigter, Bram G.A.D.H. Heijnen, Diederik Gommers, Dinis dos Reis Miranda

Resuscitation. 2019 Mar;136:8-13. doi: 10.1016

ABSTRACT

Background Cardiac arrest (CA) due to pulmonary embolism (PE) is associated with low survival rates and poor neurological outcomes. We examined whether Extracorporeal Cardiopulmonary Resuscitation (ECPR) improves the outcomes of patients who suffer from CA due to massive PE.

Methods We retrospectively included 39 CA patients with proven or strongly suspected PE in two hospitals in the Netherlands, in a 'before/after'-design. 20 of these patients were treated with Conventional Cardiopulmonary Resuscitation (CCPR) and 19 patients with ECPR.

Results The main outcomes of this study were ICU survival and favourable neurological outcome, defined as Cerebral Performance Category (CPC) score 1-2. The ICU survival rate in CCPR patients was 5% compared to 26% in ECPR patients ($p<0.01$). Survival with favourable neurological outcome was present in 0/20 (0%) CCPR patients compared to 4/19 (21%) of the ECPR patients ($p<0.05$).

Conclusion ECPR seems a promising treatment for cardiac arrest patients due to (suspected) massive pulmonary embolism compared to conventional CPR, though outcomes remain poor.

INTRODUCTION

Massive pulmonary embolism (PE) as an obstructive shock may lead to right ventricular overload and haemodynamic instability [1-3]. Eventually, this causes cardiac arrest (CA) in 32-48% of the patients [4-6]. Outcomes in CA patients due to massive PE are extremely poor, with survival rates around 0.4-18% despite urgent administration of thrombolytics [3, 7, 8].

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) decreases right ventricular overload [9] and supports the entire circulation, bypassing both lungs and heart. Especially in patients with refractory CA caused by massive PE, V-A ECMO started during cardiopulmonary resuscitation (CPR) could improve the survival. Previous studies in massive PE patients without CA showed a higher survival rate in patients who received V-A ECMO compared to conventional treatment, 83% versus 58%, respectively [9-12]. However most of these previous studies included haemodynamic unstable patients without CA or patients after CA, who regained return of spontaneous circulation (ROSC) before V-A ECMO placement. Little is known of patients cannulated during CPR.

The aim of this study is to examine whether extracorporeal cardiopulmonary resuscitation (ECPR) improves outcome of patients who suffer from CA due to massive PE. To our knowledge no previous studies were performed in CA patients due to PE, comparing CCPR with ECPR therapy. In this retrospective cohort study we analysed the data of CA patients due to (suspected) PE from two extracorporeal membrane oxygenation (ECMO) expertise centers in the Netherlands.

METHODS

We performed a retrospective study in a 'before-after' fashion in two hospitals in the Netherlands. The Erasmus MC Rotterdam (EMC) is a tertiary referral academic hospital and the Sint Antonius Hospital (SAZ) Nieuwegein is a major teaching hospital and pulmonary hypertension expertise center. Both hospitals are referral centers for cardiothoracic surgery (including surgical pulmonary embolectomy), experienced in ECMO therapy and ECPR. These hospitals started with formal implementation of ECPR therapy in August 2014.

Patients

We included adult patients treated with ECPR due to a (suspected) PE in the period of August 1st, 2014 till March 31st, 2017 (the 'after'-period). And, as a control group, we included patients treated with conventional CPR (CCPR) due to a (suspected) PE in the time period January 1st, 2012 till July 31st, 2014 (the 'before'-period).

CCPR was defined as conventional CPR, where ECPR was defined as ECMO cannulation during CPR. We defined a CA due to (suspected) PE if one of the next four criteria were present: PE proven with Computer Tomography (CT)-scan, PE proven through pathologic examination (PA), severe right ventricular dilatation during CA with a history compatible with (suspected) PE, or administration of thrombolysis during arrest due to suspicion of massive PE. We included both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) patients. The criteria for initiation of ECPR were witnessed CA (last seen < 5 min) in patients below 70 years, with good quality of basic life support (BLS) / advanced life support (ALS) (leading to an end-tidal CO2 >10 mmHg) during at least 15 min and a low flow time of <60 min.

ECMO procedure

ECMO placement in all patients of both the EMC and the SAZ, is done by intensivists, interventional cardiologists or cardiothoracic surgeons, depending of which location the CA occurs. If the CA occurs in the operating room (OR) the cardiothoracic surgeon will place it, if it occurs in the ICCU or catherization laboratory (cath. lab.), the interventional cardiologist will insert the ECMO and in all other cases the intensivists will do the ECPR procedure. The location of the ECPR will be where the patient is (e.g. OR, cath. lab., ICU, hospital ward, emergency department). There is no routine left heart catherization or left ventricular venting done in patients who receive ECMO for PE in the EMC and all ECPR patients get a 6 Fr distal reperfusion catheter of the cannulated leg, primarily implanted by the cardiothoracic or vascular surgeon.

Measured variables

Our primary outcome, ICU survival, was retrospectively collected by chart review. As a secondary outcome we analysed favourable neurological outcome. This favourable outcome was defined as a Cerebral Performance Category (CPC) score of 1-2. A CPC score of 3-5 was defined as unfavourable neurological outcome. For prospectively measuring the latter outcome, all surviving patients were contacted and asked for written informed consent and to fill in a CPC questionnaire [13].

Besides the primary and secondary outcomes, complications (e.g. bleeding [defined as major bleeding in need of transfusion/intervention or major bleeding limiting the treatment options such as thrombolysis or continuing of CPR], CVVH use, cerebral haemorrhage, vascular/ischemic limb complications and infection [defined as any infection with positive culture in general, during admission for the CCPR group and during ECMO for the ECPR group]) were included as outcome measurements and collected by chart review. These complications were only registered in Emergency Department (ED) survivors.

Statistical analysis

Continuous variables were reported using median and 25-75% quartiles and categorical variables were reported using numbers and percentages. We used the Mann-Whitney U test and a Fisher's exact test to test for statistical significant differences for continuous and categorical variables, respectively [14].

For our primary outcome ICU survival, we plotted Kaplan-Meier curves and we compared these survival distributions using the Log-rank test. For our secondary outcome, we dichotomised the CPC value into favourable outcome and unfavourable outcome.

During chart screening of the CA patients, we found some patients treated with ECPR in the 'before'-period and CCPR patients in the 'after'-period. We decided to perform a sensitivity analysis on the complete sample of CA patients due to (suspected) massive PE treated with CCPR or ECPR. One of the ECPR patients treated in the 'before'-period was >18 years at time of the questionnaire, however <18 years at time of CA. Because this patient was treated at the adult ICU, with adult cannulas, and having an 'adult' frame, we decided to include this data in the sensitivity analysis. A p-value <0.05 was defined as statistically significant. IBM SPSS Statistics version 24 was used to perform the statistical analyses.

Ethics

The Medical Ethics Committee of the ErasmusMC Rotterdam, the Netherlands, reviewed and approved the study protocol (number MEC-2017-305). All surviving patients were asked consent for participation. This consent consisted of answering the questionnaire and approving the use of their documented clinical data. For non-surviving patients, proxy consent for their chart review was not required.

RESULTS

Charts of 2618 patients were reviewed and 39 patients were included in the 'before/after'-analyses (Fig. 1). Of these 39 included patients, 20 were treated with CCPR and 19 with ECPR.

Baseline characteristics

Patients in the CCPR group were significantly older at time of CA compared to the patients in the ECPR group. In only 60% of the CCPR patients, thrombolytic therapy was given, whereas in 95% of the ECPR patients (Table 1). In the ECPR group, all but one patient were treated with thrombolytic therapy prior to ECMO cannulation. No significant differences were seen the CCPR versus ECPR groups, concerning OHCA (42% versus 68%), time between CA and start of CPR (both median 0 min), median total duration of

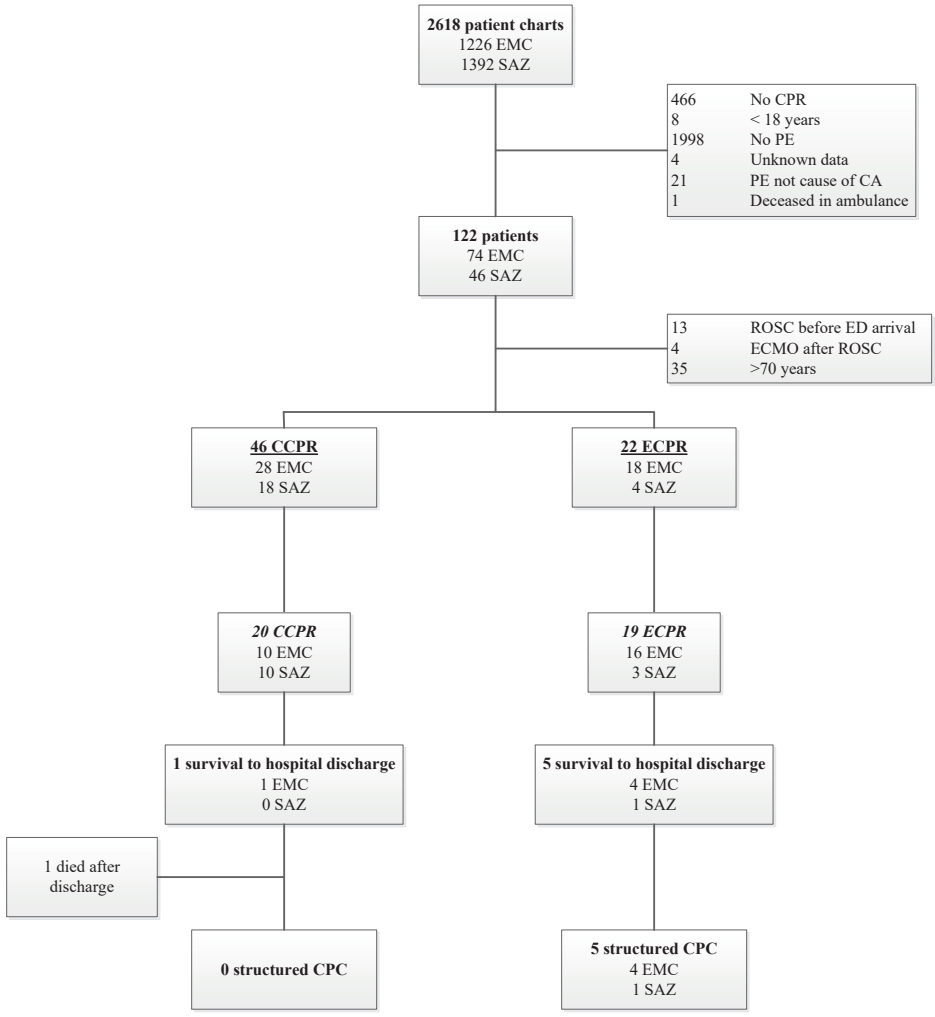


Figure 1 | Flow chart. Bold values represent the totals. The 'before/after'-analyses are done in the *italicized* patient numbers and the 'total sample'-analyses are done in the underlined patient numbers. CA cardiac arrest, CPR cardiopulmonary resuscitation, CCPR conventional cardiopulmonary resuscitation, ECPR extracorporeal cardiopulmonary resuscitation, ED emergency department, PE pulmonary embolism. EMC indicates patients from the Erasmus Medical Center, SAZ indicates patients from the Sint Antonius Hospital.

CPR (60 versus 77 min), and worst blood gas values during cardiac arrest (Table 1). The median duration of ECMO treatment in the ECPR group was 3 days (IQR 2-5 days). The median ICU length of stay in surviving ECPR patients is 19 days (IQR 10-35.5 days). In the non-surviving patients the median time on ECMO until death is 3 days (IQR 1-5 days).

Table 1 | Baseline characteristics and outcomes for CCPR versus ECPR 'before/after'

	CCPR (N=20)	*ECPR (N=19)*	*p-value*
Baseline characteristics			
Patient Characteristics			
Median Age, years (IQR)	56 (46-64)	40 (30-60)	**0.04**
Gender Male (%)	8 (40)	8 (42)	1.00
Medical history with cardiac diseases (%, total N = ECPR 19, CCPR 21)	4 (21)	0 (0)	0.11
Medical history with pulmonary diseases (%, total N = ECPR 19, CCPR 21)	5 (26)	1 (5)	0.18
Use of medication (%, total N = ECPR 18, CCPR 18)	11 (65)	11 (61)	1.00
Clinical Characteristics			
OHCA (%)	8 (42)	13 (68)	0.19
CPR delay, in minutes (IQR) (total N = CCPR 13, ECPR 18)	0 (0-0)	0 (0-2.25)	0.22
Total duration CPR, in minutes (IQR) (total N = CCPR 19, ECPR 16)	60 (45-90)	77 (39-98)	0.26
Mechanical compressions (e.g. LUCAS) (%)	7 (35)	9 (47)	0.52
Thrombolysis (%)	12 (60)	18 (95)	**0.02**
Laboratory results			
Median pH (IQR)* (total N = CCPR 15, ECPR 16)	6.85 (6.74-6.95)	6.80 (6.68-6.87)	0.28
Median PO2 in kPa (IQR)* (total N = CCPR 14, ECPR 14)	12.8 (6.2-20.7)	14.7 (3.5-26.2)	0.96
Median PCO2 in kPa (IQR)* (total N = CCPR 14, ECPR 14)	9.3 (5.8-14.4)	9. 9 (7.1-12.4)	0.96
Median lactate in mmol/L (IQR)* (total N = CCPR 14, ECPR 14)	14.3 (10.3-18.9)	14.1 (11.3-16.6)	0.91
Median arterial saturation in mol/mol (IQR)* (total N = CCPR 13, ECPR 13)	67 (43.5-96.5)	76 (16-98.5)	0.84
Outcomes			
Primary outcome			
ICU survival^	1 (5)	5 (26)	**<0.01**
Secondary outcome			
Survival with favourable neurological outcome (%)	0 (0)	4 (21)	**<0.05**
Favourable neurological outcome in ICU survivors (CCPR N=1, ECPR N=5)	0 (0)	4 (80)	0.33
Complications			
Complication; Bleeding (%)	1 (5)	14 (74)	**<0.01**
CVVH use (%)	2 (10)	7 (37)	0.07
Complication; Infection with positive culture (%)	0 (0)	5 (28)	**<0.05**
Complication; Intracranial bleeding (%)	0 (0)	2 (11)	0.23
Complication; vascular ECPR complications (%)	0 (0)	0 (0)	-

* All the median blood gas values are the worst values 6 hours before ECMO/ROSC

^As there were no differences between ICU and hospital survival, we only note the ICU survival. The p-value represents the Log-rank test.

Outcomes

A Log-rank test showed a significantly lower cumulative ICU survival in CCPR patients compared to ECPR patients (5% vs 26%, p <0.01) (Fig. 2). Survival with favourable neurological outcome was present in 0 (0%) CCPR patients versus four (21%) ECPR patients (p<0.05). Four out of five (80%) ECPR survivors had a favourable neurological outcome. One patient (20%) had severe cerebral disability with a CPC score of 3.

Furthermore, the complication rate of bleeding and infection appear more frequently in the ECPR group (p<0.05). Bleeding occurred in 5% in the CCPR group versus 74% in the ECPR group (p<0.01). A bleeding complication was documented in 13/30 (43%) of the patients who received thrombolytic therapy versus 2/9 (22%) of the patients who did not receive thrombolytic therapy (p=0.44). Of all ECPR patients, seven (37%) had access site related bleeding and two (11%) had an intracranial/cerebral haemorrhage. The other bleeding locations were abdominal, thoracic, pulmonary, and ear/nose/throat. Use of CVVH showed a trend in favour of CCPR patients and no significant difference was seen in intracranial/cerebral haemorrhage between the two groups (Table 1). Besides the access site related bleedings, no other vascular or ischemic complications due to ECPR therapy, such as limb ischemia, compartment syndromes of the legs or fasciotomies occurred.

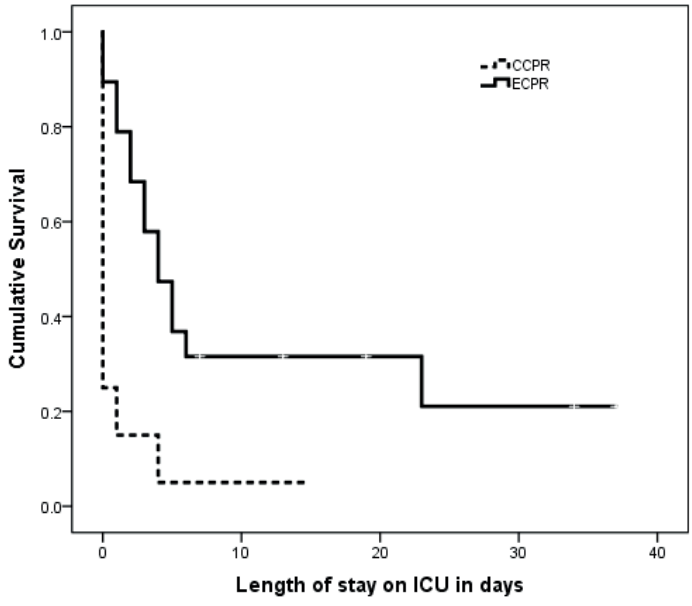


Figure 2 | Survival curve for CCPR versus ECPR of the 'before/after' analysis (n=39)

When performing the analyses on only the patients treated with thrombolytic therapy, we found comparable results. The cumulative ICU survival was 8% in CCPR patients vs 28% in ECPR patients (p<0.01) with a survival with favourable neurological outcome of 0% vs 22% respectively (p=0.13).

Sensitivity analysis

In our sensitivity analysis, we included the 39 patients from the 'before/after'-setting, the remaining three ECPR patients from the 'before'-period, and the remaining 26 CCPR patients from the 'after'-period. The reasons why the CCPR patients of the 'after'-group included in sensitivity analysis were not treated with ECPR therapy are explained in Supplementary material, Table 3. Of the total 68 included patients, 46 patients had CCPR and 22 patients got treatment with ECPR therapy.

The baseline characteristics of the total sample were comparable to the results of the 'before/after'-setting. The only difference, was a significantly higher percentage of patients with a medical history of pulmonary disease prior to the CA in the CCPR group in comparison with the ECPR group, 26% (n=11) versus 5% (n=1), respectively (p<0.05) (Supplementary material, Table 2). This pulmonary disease consisted of Chronic Obstructive Pulmonary Disease (COPD), pulmonary emphysema, bronchial asthma, mesothelioma, pulmonary metastasis of colon carcinoma, pulmonary metastasis of breast cancer, stage IV pulmonary carcinoma, or pulmonary embolism. Table 4 in Supplementary material shows the diagnostics used to confirm/suspect diagnosis of PE.

The primary and secondary outcome results of the sensitivity analysis were also comparable to the results of the 'before/after'-setting (Table 2 and Fig 3, Supplementary material). There were two notable differences. First, the difference in survival with favourable neurological outcome between the CCPR and ECPR groups became nonsignificant (Table 2, Supplementary material). However a trend to significance remained, with a p-value of 0.05. Second, the trend in the use of CVVH became significantly lower in CCPR versus ECPR patients (Table 2, Supplementary material). The reasons for death in non-survivors in this study in the CCPR group (n=41, out of total n=46) mostly because of unsuccessful resuscitation (n=39) and two because of neurological reasons. Most of the ECPR patients (total n=22) died from neurological causes (n=11), e.g. brain death or termination of treatment due to poor neurological prognosis. Two patients died from multi-organ failure and two from haemorrhagic shock.

DISCUSSION

The present study showed that patients with CA due to (suspected) massive PE treated with CCPR had a lower ICU survival rate and a worse favourable neurological outcome as

compared to patients treated with ECPR. To our knowledge, this is the first retrospective study that attempts to compare the survival and neurological outcomes of the CCPR and ECPR treatments in (suspected) PE patients.

In line with previous studies in CA patients due to massive PE, the survival rate of our control group (CCPR group) was very low (5%). Er et al. [15] showed a somewhat higher survival rate of 18.3%, but they included only IHCA patients. Comess et al. [16] also found a slightly higher survival rate (22.2%). However, only patients with unknown reason for CA received a transoesophageal echocardiography (TEE) and were included in their study. Thereby they excluded the other CA patients due to PE, what probably resulted in selection bias. Leitner et al. [17] included only patients that received thrombolytic agents and found a survival rate of 19%.

In contrast, two other studies found lower survival rates. In a study comparing thrombolytic therapy against no thrombolytic therapy in CA due to PE, Yousuf et al. [8] found a combined survival rate of 9.5% (10.5% vs 8.7%, respectively). In a slightly larger study, Kürkciyan et al. [7] also compared thrombolysis versus no thrombolysis in CA due to PE. This study showed a survival rate of 5% [7]. These rates are comparable with our controls, with a survival rate of 5% in the CCPR group in the 'before/after' design and 11% in the total sample. Previous studies concerning thrombolytic therapy in CA patients due to PE, show both significantly and non-significantly lower survival rates in patients not treated with thrombolytic agents [8, 18]. Thus, the significant difference in administration of thrombolytic therapy in our study, may contribute to the difference in survival outcomes between the two groups.

The survival rate in our ECPR group is comparable with previous studies [9, 11, 19-23]. Although, the survival rates in studies describing V-A ECMO after massive PE show large variation [9, 11, 19-23]. In these studies, demonstrating a relatively high survival rate (25-83%), only patients who regained ROSC before implantation of V-A ECMO were included [9, 11, 19-23]. In other studies examining V-A ECMO during resuscitation, survival rates were between 0 and 60%, however, these studies only included between two and seven patients [24-26]. Two recent, larger studies [27, 28] showed a survival rate of 38.5-46% in patients with cardiogenic shock or CA due to massive PE. In contrast with those studies, we did not include patients with ROSC before ECMO placement.

Patients who are treated with ECPR for cardiac arrest due to PE, seem to have a good neurological outcome. Pasrija et al. [23] found a good neurological outcome in both of the ECPR patients included in their study. A slightly larger study by Hashiba et al. [11] included 12 patients with CA due to PE who received V-A ECMO. 6 patients were treated with ECPR and 6 patients treated with V-A ECMO after ROSC. They found a CPC-score of 1-2 at discharge in 70% of the surviving patients [11], comparable to our results with 80% of the survivors having a favourable neurological outcome.

There are several limitations to this study, related to the observational design that need to be addressed. First, two potential biases that may influence the generalizability of the results are confounding by indication and selection bias. The three patients in the 'before'-period who were treated with ECPR. The decision to treat with ECPR took place at the discretion of the clinical physician present. We tried to minimize these two biases as much as possible by performing a pure 'before/after'-analysis and a sensitivity analysis with the total sample of CCPR and ECPR patients. This sensitivity analysis showed similar results in comparison with the 'before/after'-analysis which reduces the selection bias.

Second, we tried to establish two comparable and homogeneous groups by excluding all patients above 70 years old of the CCPR group. However, we were not able to perform propensity matching, nor multivariate analysis due to the small sample size. To minimize confounding by indication as well as countering the limitations of this study, a randomized controlled trial is required in the future.

Next, diagnosis of PE in patients without ROSC is difficult. Therefore, we defined criteria which had to be met, to apply for the diagnosis suspected PE as closest approximation of the diagnosis PE during CA. To obtain a definitive diagnosis PE, a CT-scan, ventilation-perfusion scan or pulmonary angiography is needed, which was not feasible in CA patients without ROSC. In our study, only one patient had a history of (stable) decreased RV function. However, this patient had a cardiac arrest 20 days after a surgical procedure, therefore we included this patient with diagnosis high suspicion of PE. All other included patients had no known history of RV failure/dilatation.

Another important limitation of this study is the relative small sample size and thereby the inability of performing any modelling in which probable confounders (i.e., the application of thrombolytic therapy) could be included. Therefore, in the future it is necessary to perform a study in a larger sample size, to measure the effect of confounders.

Thus, ECPR therapy has promising results in comparison with the CCPR therapy, although the overall survival rate in the ECPR group remains low and significant complications may occur. With this study we have shown that a large percentage of patients who survive using ECPR, have a favourable neurological outcome. With these results, and taking the high risk of complications into account, ECPR could be a potential treatment option in CA patients due to (suspected) PE.

CONCLUSION

In our two-center experience, we conclude that survival rate and favourable neurological outcome in patients with CA due to (suspected) massive PE is improved using ECPR

as compared to CCPR. However, further research is needed in larger samples to confirm these encouraging findings.

REFERENCES

1. Fedullo PF, Yung GL. Pulmonary Thromboembolic Disease. In: Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, et al., editors. Fishman's Pulmonary Diseases and Disorders, 5e. New York, NY: McGraw-Hill Education; 2015.
2. Aissaoui N, Konstantinides S, Meyer G. What's new in severe pulmonary embolism? Intensive Care Med. 2018.
3. Logan JK, Pantle H, Huiras P, Bessman E, Bright L. Evidence-based diagnosis and thrombolytic treatment of cardiac arrest or periarrest due to suspected pulmonary embolism. Am J Emerg Med. 2014;32:789-96.
4. Bailen MR, Cuadra JA, Aguayo De Hoyos E. Thrombolysis during cardiopulmonary resuscitation in fulminant pulmonary embolism: a review. Crit Care Med. 2001;29:2211-9.
5. Kadner A, Schmidli J, Schonhoff F, Krahenbuhl E, Immer F, Carrel T, et al. Excellent outcome after surgical treatment of massive pulmonary embolism in critically ill patients. J Thorac Cardiovasc Surg. 2008;136:448-51.
6. Tokyo CCUNSC. Latest management and outcomes of major pulmonary embolism in the cardiovascular disease early transport system: Tokyo CCU Network. Circ J. 2010;74:289-93.
7. Kurkciyan I, Meron G, Sterz F, Janata K, Domanovits H, Holzer M, et al. Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. Arch Intern Med. 2000;160:1529-35.
8. Yousuf T, Brinton T, Ahmed K, Iskander J, Woznicka D, Kramer J, et al. Tissue Plasminogen Activator Use in Cardiac Arrest Secondary to Fulminant Pulmonary Embolism. J Clin Med Res. 2016;8:190-5.
9. Maggio P, Hemmila M, Haft J, Bartlett R. Extracorporeal life support for massive pulmonary embolism. J Trauma. 2007;62:570-6.
10. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353:1386-9.
11. Hashiba K, Okuda J, Maejima N, Iwahashi N, Tsukahara K, Tahara Y, et al. Percutaneous cardiopulmonary support in pulmonary embolism with cardiac arrest. Resuscitation. 2012;83:183-7.
12. Yusuff HO, Zochios V, Vuylsteke A. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a systematic review. Perfusion. 2015;30:611-6.
13. Mak M, Moulaert VR, Pijls RW, Verbunt JA. Measuring outcome after cardiac arrest: construct validity of Cerebral Performance Category. Resuscitation. 2016;100:6-10.
14. Field A. Discovering statistics using SPSS. Third ed: Sage Publications; 2009.
15. Er F, Nia AM, Gassanov N, Caglayan E, Erdmann E, Hoppe UC. Impact of rescue-thrombolysis during cardiopulmonary resuscitation in patients with pulmonary embolism. PLoS One. 2009;4:e8323.
16. Comess KA, DeRook FA, Russell ML, Tognazzi-Evans TA, Beach KW. The incidence of pulmonary embolism in unexplained sudden cardiac arrest with pulseless electrical activity. Am J Med. 2000;109:351-6.
17. Leitner JM, Jilma B, Spiel AO, Sterz F, Laggner AN, Janata KM. Massive pulmonary embolism leading to cardiac arrest is associated with consumptive coagulopathy presenting as disseminated intravascular coagulation. J Thromb Haemost. 2010;8:1477-82.
18. Spohr F, Wenzel V, Bottiger BW. Thrombolysis and other drugs during cardiopulmonary resuscitation. Curr Opin Crit Care. 2008;14:292-8.
19. Bougouin W, Marijon E, Planquette B, Karam N, Dumas F, Celermajer DS, et al. Pulmonary embolism related sudden cardiac arrest admitted alive at hospital: Management and outcomes. Resuscitation. 2017;115:135-40.

20. George B, Parazino M, Omar HR, Davis G, Guglin M, Gurley J, et al. A retrospective comparison of survivors and non-survivors of massive pulmonary embolism receiving veno-arterial extracorporeal membrane oxygenation support. Resuscitation. 2018;122:1-5.
21. Munakata R, Yamamoto T, Hosokawa Y, Tokita Y, Akutsu K, Sato N, et al. Massive pulmonary embolism requiring extracorporeal life support treated with catheter-based interventions. Int Heart J. 2012;53:370-4.
22. Omar HR, Miller J, Mangar D, Camporesi EM. Experience with extracorporeal membrane oxygenation in massive and submassive pulmonary embolism in a tertiary care center. Am J Emerg Med. 2013;31:1616-7.
23. Pasrija C, Kronfli A, George P, Raithel M, Boulos F, Herr DL, et al. Utilization of Veno-Arterial Extracorporeal Membrane Oxygenation for Massive Pulmonary Embolism. Ann Thorac Surg. 2018;105:498-504.
24. Swol J, Buchwald D, Strauch J, Schildhauer TA. Extracorporeal life support (ECLS) for cardiopulmonary resuscitation (CPR) with pulmonary embolism in surgical patients - a case series. Perfusion. 2016;31:54-9.
25. Corsi F, Lebreton G, Brechot N, Hekimian G, Nieszkowska A, Trouillet JL, et al. Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation. Crit Care. 2017;21:76.
26. Kawahito K, Murata S, Adachi H, Ino T, Fuse K. Resuscitation and circulatory support using extracorporeal membrane oxygenation for fulminant pulmonary embolism. Artif Organs. 2000;24:427-30.
27. Meneveau N, Guillon B, Planquette B, Piton G, Kimmoun A, Gaide-Chevronnay L, et al. Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases. Eur Heart J. 2018.
28. Al-Bawardy R, Rosenfield K, Borges J, Young MN, Albaghdadi M, Rosovsky R, et al. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a case series and review of the literature. Perfusion. 2018:267659118786830.

SUPPLEMENTARY MATERIAL

Table 2 | Baseline characteristics and outcomes for CCPR versus ECPR total sample

	CCPR (N=46)	*ECPR (N=22)*	*p-value*
Baseline characteristics			
Patient Characteristics			
Median Age, years (IQR)	57 (51-63)	40 (30-59)	**<0.01**
Gender Male (%)	23 (508)	9 (41)	0.61
Medical history with cardiac diseases (%, total N = CCPR 42, ECPR 22)	6 (14)	0(0)	0.09
Medical history with pulmonary diseases (%, total N = CCPR 42, ECPR 22)	11 (26)	1 (5)	**<0.05**
Use of medication (%, total N = CCPR 37, ECPR 21)	25 (68)	12 (57)	0.57
Clinical Characteristics			
OHCA (%)	26 (58)	14 (64)	0.79
CPR delay, in minutes (IQR) (total N = CCPR 28, ECPR 21)	0 (0-0)	0 (0-0)	0.47
Total duration CPR, in minutes (IQR) (total N = CCPR 44, ECPR 19)	68 (34-90)	70 (38-93)	0.88
Mechanical compressions (%)	16 (37)	9 (41)	0.79
Thrombolysis (%)	27 (59)	19 (86)	**>0.03**
Laboratory results			
Median pH (IQR)* (total N = CCPR 38, ECPR 19)	6.79 (6.70-6.94)	6.8 (6.73-6.99)	0.67
Median PO2 in kPa (IQR)* (total N = CCPR 37, ECPR 19)	7.3 (4.1-15.4)	10.6 (3.6-23.7)	0.24
Median PCO2 in kPa (IQR)* (total N = CCPR 37, ECPR 17)	10.3 (7.3-13.9)	9.2 (6.6-12.2)	0.15
Median lactate in mmol/L (IQR)* (total N = CCPR 34, ECPR 17)	14.2 (10.9-17.9)	14.8 (11.2-16.6)	0.95
Median arterial saturation in mol/mol (IQR)* (total N = CCPR 35, ECPR 16)	58 (17-86)	82.5 (18.3-98.8)	0.13
Outcomes			
Primary outcome			
ICU survival (%)^	5 (11)	7 (32)	**<0.01**
Secondary outcome			
Survival with favourable neurological outcome (%) (total N CCPR = 45)	3 (7)	6 (27)	0.05
Favourable neurological outcome in ICU survivors (ECPR N=7, CCPR N=4)	3 (75)	6 (86)	1.00
Complications			

Table 2 | Baseline characteristics and outcomes for CCPR versus ECPR total sample (*continued*)

	CCPR (N=46)	***ECPR (N=22)***	***p-value***
Complication; Bleeding (%)	4 (9)	15 (68)	**<0.01**
CVVH use (%)	4 (9)	7 (32)	**0.03**
Complication; Infection with positive culture (%)	1 (2)	5 (24)	**0.01**
Complication; Intracranial bleeding (%)	0 (0)	2 (9)	0.10
Complication; vascular ECPR complications (%)	0 (0)	0 (0)	-

* All the median blood gas values are the worst values 6 hours before ECMO/ROSC
^As there were no differences between ICU and hospital survival, we only note ICU survival. The p-value represents the Log-rank test.

Table 3 | Reasons for exclusion of ECMO therapy in cases with CCPR after implementation of ECPR

Patient	**Reason for CCPR therapy after initiation of ECPR protocol**
1	CPR time > 60 minutes
2	CPR time > 60 minutes
3	Malignancy with metastasis, palliative therapy
4	PCO2 < 1.3
5	PE found at pathology, no high PE suspicion during CPR
6	Poor physical condition, nursery home
7	Because of suspicion CVA contraindication for ECMO
8	Long CPR time in combination with very poor arterial blood gas values
9	Long delay until start CPR
10	ECMO not available, due to cannulation of other patient at the same moment
11	Cannulated during CPR, ROSC before starting ECMO flow
12	CPR time > 60 minutes
13	Malignancy
14	CPR time > 60 minutes, non-witnessed arrest with long delay until CPR
15	Long delay until start CPR
16	Malignancy
17	Reason for admission cerebral bleeding (contra-indication ECMO)
18	Malignancy
19	Long CPR time in combination with very poor initial arterial blood gas values
20	Decompensated liver cirrosis
21	Malignancy with metastasis
22	Malignancy
23	CPR time > 60 minutes
24	ROSC before initiation ECPR
25	ROSC before initiation ECPR
26	Unknown delay until CPR

Table 4 | Diagnostics used to confirm diagnosis of PE

	EMC		SAZ		Total
	ECPR	**CCPR**	**ECPR**	**CCPR**	
CT-proven	16	8	2	2	28
OR-proven	1	0	0	0	1
PA-proven	1	4	0	5	10
TEE/TTE (thrombus)	1	1	0	0	2
TEE/TTE (dilated RV)	0	11	1	10	22
No diagnostics	0	4	0	1	5

CT = computer tomography, OR = operating room, PA = pathology, TEE = transoesophageal echocardiogram, TTE = transthoracic echocardiogram, RV = right ventricle

The 5 patients in whom no diagnostics were done, are included in the study because of administration of thrombolysis during CA due to suspicion of massive PE. These patients had a suspicion for pulmonary embolism with: ECG showing signs pointing to PE, other causes for CA excluded, or the prognosis was so poor that diagnosing would not influence the therapeutic options. This table was made in order of probability of PE. In the cases of a CT-proven PE, OR/PA/TTE/TEE would not be scored again.

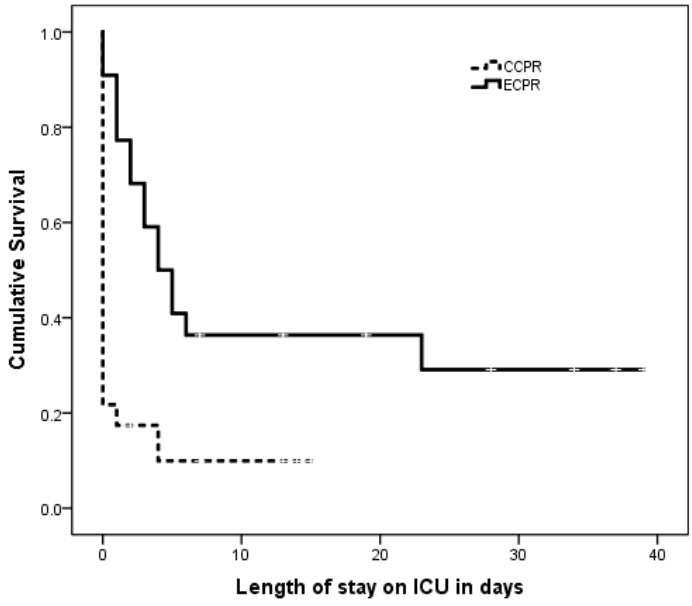


Figure 3 | Survival curve for CCPR versus ECPR of the total sample (n=68)

Chapter 9

Survival of patients with acute pulmonary embolism treated with venoarterial extracorporeal membrane oxygenation: A systematic review and meta-analysis

Mina Karami*, Loes Mandigers*, Dinis Dos Reis Miranda, Wim J.R. Rietdijk, Jan M. Binnekade, Daniëlle C.M. Knijn, Wim K. Lagrand, Corstiaan A. den Uil, José P.S. Henriques, Alexander P.J. Vlaar. On behalf of the DUTCH ECLS Study Group
* contributed equally

Journal of Critical Care. 2021 Mar, https://doi.org/10.1016/j.jcrc.2021.03.006

ABSTRACT

Background To examine whether venoarterial extracorporeal membrane oxygenation (VA-ECMO) improves survival of patients with acute pulmonary embolism (PE).

Methods Following the PRISMA guidelines, a systematic search was conducted up to August 2019 of the databases: PubMed/MEDLINE, EMBASE and Cochrane. All studies reporting the survival of adult patients with acute PE treated with VA-ECMO and including four patients or more were included. Exclusion criteria were: correspondences, reviews and studies in absence of a full text, written in other languages than English or Dutch, or dating before 1980. Short-term (hospital or 30-day) survival data were pooled and presented with relative risks (RR) and 95% confidence intervals (95% CI). Also, the following pre-defined factors were evaluated for their association with survival in VA-ECMO treated patients: age > 60 years, male sex, pre-ECMO cardiac arrest, surgical embolectomy, catheter directed therapy, systemic thrombolysis, and VA-ECMO as single therapy.

Results A total of 29 observational studies were included (N = 1947 patients: VA-ECMO N = 1138 and control N = 809). There was no difference in short-term survival between VA-ECMO treated patients and control patients (RR 0.91, 95% CI 0.71–1.16). In acute PE patients undergoing VA-ECMO, age > 60 years was associated with lower survival (RR 0.72, 95% CI 0.52–0.99), surgical embolectomy was associated with higher survival (RR 1.96, 95% CI 1.39–2.76) and pre-ECMO cardiac arrest showed a trend toward lower survival (RR 0.88, 95% CI 0.77–1.01). The other evaluated factors were not associated with a difference in survival.

Conclusions At present, there is insufficient evidence that VA-ECMO treatment improves short-term survival of acute PE patients. Low quality evidence suggest that VA-ECMO patients aged ≤60 years or who received SE have higher survival rates. Considering the limited evidence derived from the present data, this study emphasizes the need for prospective studies.

Protocol registration: PROSPERO CRD42019120370.

Keywords: Pulmonary embolism, Extracorporeal membrane oxygenation, Extracorporeal life support, Hemodynamic instability, Cardiac arrest, ECPR

INTRODUCTION

Massive pulmonary embolism (PE) is associated with poor survival. The obstructive shock caused by massive PE can result in end-organ failure and cardiac arrest [1,2]. Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO) is increasingly used as a treatment strategy in hemodynamically compromised patients with acute PE. VA-ECMO restores the circulation and unloads the right ventricle by bypassing the pulmonary circulation. While circulation is restored, the PE can resolve or be removed. So, in case of acute PE, VA-ECMO may be used as bridge to recovery or bridge to treatment.

Although VA-ECMO enables haemodynamic stability and restores tissue perfusion, it is unknown if this high-risk therapy will lead to higher survival rates in acute PE patients. In addition, it is not clear which patients would benefit the most and for which patients this highly invasive therapy with major complication rate would not be a suitable treatment option.

In an attempt to investigate whether VA-ECMO treatment is beneficial and if there are any factors associated with clinical outcome, we performed a systematic review and meta-analysis on the current available evidence. The aim of this study is to examine whether VA-ECMO treatment is associated with an improved survival in acute PE patients and to explore factors that may be associated with survival.

MATERIALS AND METHODS

This study is performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [3]. It is listed in the PROSPERO register with registration number CRD42019120370.

Study eligibility criteria

To qualify for inclusion studies had to include adults (≥ 18 years) with acute PE of any aetiology who received VA-ECMO treatment. We also included studies that only contained a subgroup of acute PE patients with VA-ECMO. A control group (defined as acute PE patients without VA-ECMO treatment) was not necessary to qualify for inclusion. Studies were only included if they reported the primary outcome (short-term survival) for PE patients that received VA-ECMO. Any type of study (e.g., randomized trial, observational cohort, case-control, case-series) containing four patients or more was included. Exclusion criteria were studies that only involved patients with cardiac arrest or shock due to other aetiologies than PE. Further, correspondences, reviews and studies in absence of a full text, written in other languages than English or Dutch or dating before 1980 were also excluded.

Search

A medical information specialist conducted a systematic search of the following databases: PubMed/MEDLINE (OVID), EMBASE (OVID) and the Cochrane Central Register of Controlled Trials (CENTRAL) up to 5 August 2019. The full search is available in the Additional file Appendix 1. In summary, we integrated various search terms containing 'extracorporeal life support' combined with 'pulmonary embolism' applying the Boolean operator 'AND' using medical subject headings (Mesh) and free terms. Synonyms were added to the search: 'Extracorporeal membrane oxygenation' or 'ECMO' or 'ECLS' combined with 'pulmonary thromboembolism' using the Boolean operator 'OR' to screen on various synonyms.

Study selection

Two reviewers (M.K. and L.M.) independently screened all titles and abstracts. After selecting articles for full text screening, they discussed any disagreements regarding inclusion or exclusion. Next, these selected papers were independently screened (by M.K. and L.M.) in full text and if they met the selection criteria, they were included for data extraction. Disagreements concerning inclusion or exclusion for this review were discussed and when needed a third reviewer (A.V.) was consulted. All of the disagreements regarding eligibility were resolved.

Definitions

The primary outcome was short-term survival, defined as hospital or 30-day survival. Long-term survival was defined as ≥3-month survival. Favourable neurological outcome was defined as a cerebral performance category (CPC) score of 1–2. As secondary outcome, factors were evaluated for their association with survival in patients treated with VA-ECMO. The following pre-defined factors were evaluated: age > 60 years, male sex, cardiac arrest occurring pre ECMO initiation or during ECMO initiation (i.e., extracorporeal cardiopulmonary resuscitation, ECPR), surgical embolectomy, catheter directed therapy (i.e., thrombectomy or thrombolysis, CDT), systemic thrombolysis and VA-ECMO as single therapy.

Data extraction

Two reviewers (M.K. and L.M.) extracted the data independently, using a pre-defined standardized data extraction form. Extracted data were compared and in case of discrepancies the original articles were checked. The pre-defined data extraction included: study characteristics (e.g., author and study design), number of PE patients (categorized in VA-ECMO and control), patient demographics (e.g., age and sex), baseline characteristics (e.g., predisposing factors and extracorporeal cardiopulmonary resuscitation, ECPR), treatment characteristics (e.g., systemic thrombolysis and surgical embolectomy),

clinical course (e.g., complications) and clinical outcomes (e.g., survival and neurological outcome). We classified study design as descriptive study or cohort study as described by Grimes et al. [4]

For the meta-analyses on factors associated with outcome, data were collected from studies that reported individual patient outcomes of patients treated with VA-ECMO (survivors and non-survivors). In case data were missing regarding the evaluated factors, we attempted to obtain this information by contacting the first author.

Quality assessment

The quality of the individual studies and the certainty of evidence were assessed by two independent reviewers (M.K. and L.M.). The overall quality / certainty of evidence was rated using the GRADE's approach. [5] All included studies had an observational design and were therefore evaluated using the Newcastle-Ottawa Scale (NOS) for the individual quality assessment of non-randomized studies [6]. The NOS is a 'star-rating system' divided in to three sections: the selection of the study groups (max. 4 stars); the comparability of the groups (max. 2 stars); and the ascertainment of respectively, either the exposure or outcome of interest for case-control or cohort studies (max. 3 stars). The NOS scoring system is classified as: poor quality 0–3 stars; fair quality 4–6 stars, good quality 7–9 stars. Discrepancies were resolved by discussion.

Statistical analysis

First, we narratively described study, patient, clinical characteristics, and outcomes for each included study. Studies were categorized as VA-ECMO with control or, only VA-ECMO patients without a control group. Continuous variables were reported using mean and standard deviation (SD) or median and 25–75% quartiles (IQR) where applicable. Categorical variables were reported using numbers and percentages.

Second, for the meta-analysis involving all controlled studies, association with survival was evaluated by calculating the pooled risk ratio (RR) with 95% confidence interval (95% CI). The RRs were compared using the random-effects model and the Der-Simonian and Laird method. Because of the presence of multiple zero cells, a value of 0.5 was added to each cell. Forest plots were provided for our primary outcome (short-term survival) and secondary outcome (factors evaluated for their association with survival in patients treated with VA-ECMO).

Third, in a pre-defined additional analysis we divided patients in three subgroups: [1] Patients with obstructive shock before ECMO placement; [2] Patients who experienced a cardiac arrest before or during ECMO placement; [3] these cardiac arrest patients were further divided in patients with ROSC before or during ECMO placement and patients without ROSC during ECMO placement (i.e., ECPR) patients. A loss of output and/or pulsatility during ECMO treatment was not taken into account in these subgroups. To

estimate summary effects sizes, we used a single column meta-analysis technique. We synthesized a weighted average proportion (effect size) by using a random effects model. Due to the small sample size and some extreme proportions, we used a double-arcsin transformation on the data. The forest plot data were back transformed to proportions. With this analysis we attempted to decrease the heterogeneity between studies.

For these meta-analyses, heterogeneity was assessed using I2 and Tau2 statistics. In accordance with the Cochrane handbook, an I2 of more than 40% was classified as substantial heterogeneity. [7] Egger regression tests and funnel plots were provided to assess publication bias. A sensitivity analysis was performed to check if outlying studies influenced our results. In the factors that contained outliers, additional analysis with exclusion of these studies was performed. A two-sided p-value of ≤0.05 was considered statistically significant, except for Egger regression test in which a two-sided p-value of ≤0.10 was considered statistically significant. We performed all analyses using the Meta package in R studio, version 3.6.0.

RESULTS

Study selection

A total of 913 unique articles were retrieved during our search. We assessed 91 articles full text for eligibility and included 29 articles for this review, of which 24 articles reported individual patient outcome data and were included in the meta-analysis [[8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36]]. All included studies had an observational design. The reasons for exclusion of the articles are listed in Fig. 1. Overall, a total number of 1947 acute PE patients were included in the studies. Of these patients, 1138 received VA-ECMO treatment and 809 patients did not receive VA-ECMO treatment (control group). In the studies which reported the predefined subgroups, 143 patients were reported as being in shock and 511 patients suffered a cardiac arrest, of whom 106 patients received ECPR. The criteria and indications for the decision to initiate VA-ECMO in the included studies are available in Additional file Table A. (See Fig. 2.)

Characteristics

Study characteristics are shown in Additional file Table B for the included studies. There were 20 descriptive studies and 9 retrospective cohort studies. Patient characteristics of acute PE patients treated with VA-ECMO and control patients are shown in the Additional file Table C. The clinical course of patients is shown in Table 1.

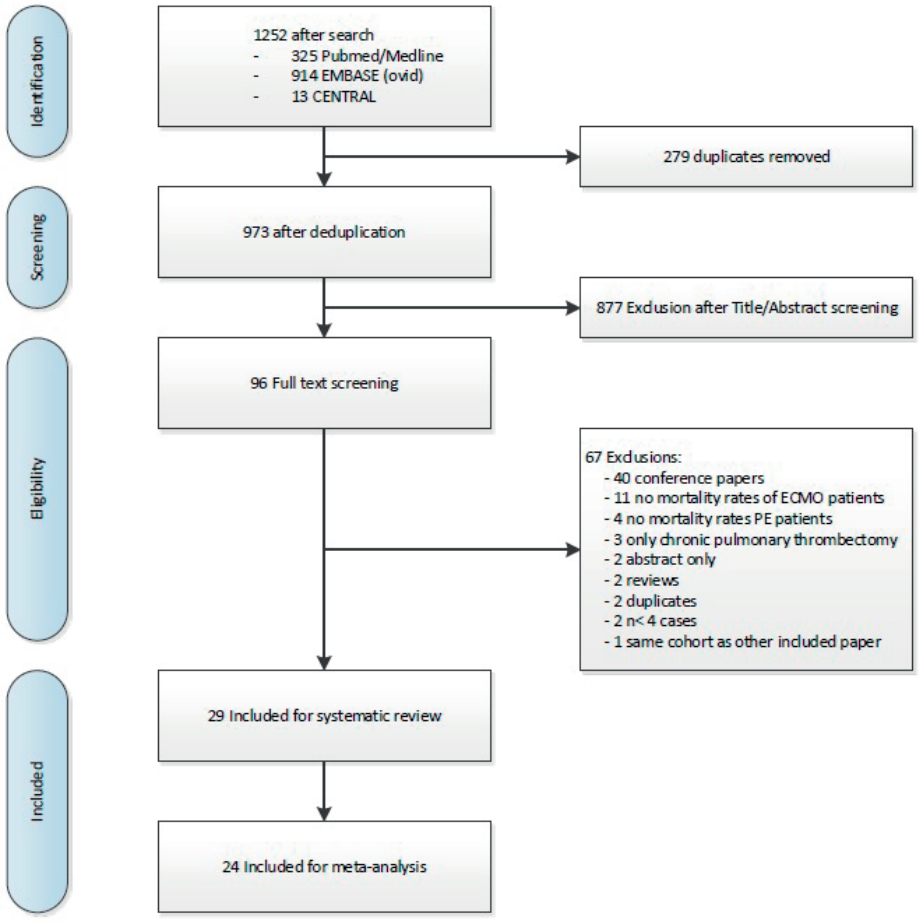


Figure 1 | Flowchart of study selection using PRISMA guidelines.

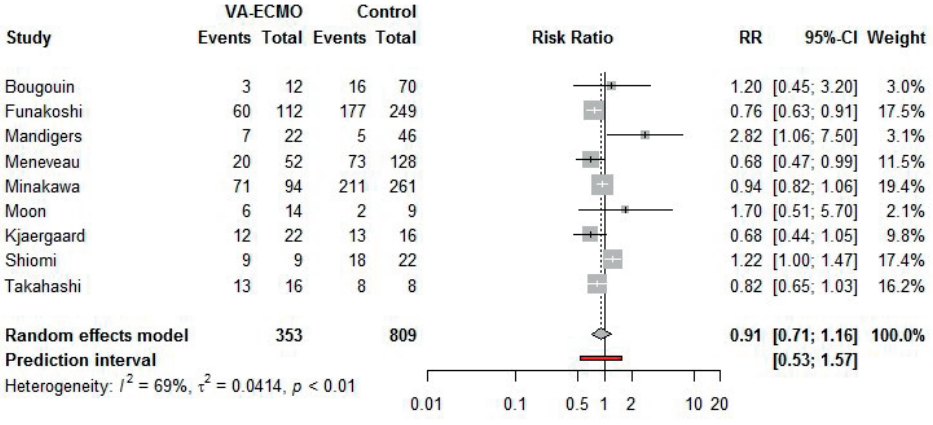


Figure 2 | Short-term survival of VA-ECMO and control patients.

Table 1 | Clinical course of massive pulmonary embolism patients treated with/without VA-ECMO.

Studies including VA-ECMO and control patients

		Number of PE patients		Shock (n, %)		Cardiac arrest (n, %)		ECPR (n, %)
	Study	**VA-ECMO**	**Control**	**VA-ECMO**	**Control**	**VA-ECMO**	**Control**	**VA-ECMO**
3	Bougouin	12	70			12 (100)	70 (100)	
8	Funakoshi	112	249			48 (43)	45 (18)	
13	Mandigers	22	46			22 (100)	46 (100)	22 (100)
14	Meneveau	52	128	13 (25)	58 (45)	39 (75)	45 (35)	18 (35)
15	Minakawa	94	261					
16	Moon	14	9	2 (21)	1 (11)	11 (79)	8 (89)	
24	Kjaergaard	22	16	5 (23)	14 (88)	22 (100)	0 (0)	22 (100)
25	Shiomi	9	22					
26	Takahashi	16	8			11 (69)	0 (0)	

Studies including only VA-ECMO patients, without control group

		Number of PE patients	Shock (n, %)	Cardiac arrest (n, %)	ECPR (n, %)	Reperfusion therapy (type, n, %)		
	Study	**VA-ECMO**	**VA-ECMO**	**VA-ECMO**	**VA-ECMO**			
						Surgical Embolectomy	*CDT*	*Systemic thrombolysis*
1	Al-Bawardy	13	13 (100)	13 (100)		4 (31)	3 (23)	8 (62)
2	Aso	353						
4	Corsi	17	2 (12)	15 (82)	7 (41)	2 (12)	2 (12)	8 (47)
5	de Chambrun	4	4 (100)	4 (100)	0 (0)			
6	Dennis	5		5 (100)	5 (100)			
7	Dolmatova	5	5 (100)	4 (80)		1 (20)	2 (40)	3 (60)
9	George	32		15 (47)		2 (6)	19 (59)	5 (16)
10	Kawahito	7	1 (14)	5 (71)	5 (71)	3 (43)		7 (100)
11	Maggio	19	11 (58)	10 (53)	8 (42)	4 (21)	7 (37)	6 (32)
12	Malekan	4	3 (75)					
17	Munakata	10	1 (10)	9 (90)		8 (80)	8 (80)	2 (20)
18	Omar	4	3 (75)	2 (50)		2 (50)	2 (50)	
19	Pasrija	20		5 (25)	2 (10)	11 (55)	1 (5)	7 (35)
20	Swol	5		5 (100)	5 (100)	2 (40)		3 (60)
21	Sakuma	7		5 (71)		1 (14)	1 (14)	6 (86)
22	Hashiba	12		12 (100)	6 (50)		4 (33)	6 (50)
23	Maj	6		6 (100)	6 (100)	1 (17)	2 (33)	2 (33)
27	Tayama	7	7 (100)	2 (29)		5 (71)		6 (86)
28	Ius	36		15 (42)		20 (56)		19 (53)
29	Elbadawi	219				45 (20.4)		54 (24.9)

VA-ECMO = veno arterial extracorporeal membrane oxygenation, PE = pulmonary embolism,
ECPR = extracorporeal cardiopulmonary resuscitation
CDT = catheter directed thrombectomy/thrombolysis
RVAD = right ventricular assist device, AKI = acute kidney injury, CVVH = continuous veno venous hemofiltration

Reperfusion therapy (type, n, %)			**Complications (type, n, %)**				
Surgical Embolectomy	*CDT*	*Systemic thrombolysis*	*Bleeding*	*Neurological (incl bleeding)*	*Infection*	*AKI/ CVVH*	*Other*
29 (26)		83 (74)					
		19 (86)	13 (59)	2 (9)	5 (24)	7 (32)	
17 (33)		20 (38)	20 (39)	4 (8)	24 (46)	22 (42)	27 (52)
1 (7)		1 (7)					
5 (23)	1 (5)	12 (55)	3 (14)	2 (9)			VA-ECMO problems 1 (5)
16 (100)			3 (19)				

Reperfusion therapy (type, n, %)	**Complications (type, n, %)**					
Other	*Bleeding*	*Neurological (incl bleeding)*	*Infection*	*AKI/CVVH*	*VA-ECMO problems*	*Other*
	7 (54)					2 (15)
	15 (88)	4 (24)	2 (12)	13 (76)		2 (12)
		1 (20)				3 (60)
	11 (34)					
	14 (74)	5 (24)	5 (24)	5 (24)	3 (14)	15 (79)
	4 (100)					
	10 (100)		1 (10)			
RVAD 1 (25)						
	2 (10)			4 (20)		1 (5)
Only VA ECMO 1 (20)	3 (60)	1 (20)			2 (40)	
	6 (50)					
	2 (33)	1 (17)	1 (17)		1 (17)	3 (50)
	3 (43)					1 (14)
	3 (8)	2 (6)		5 (14)		10 (28)
	59 (27)				144 (66)	

Complications

Twelve of the included studies reported complication rates. The classifications/definitions of complications were not reported (most studies) or heterogeneous among the studies. In the Additional file Table D the classification of complications of individual studies is reported. The incidence of complications differed widely, as shown in Table 1. Bleeding occurred in 8–100% of the patients, neurological complications (including neurological bleeding) in 8–76%, AKI/CVVH in 14–76%, and VA-ECMO problems in 5–66% of the patients.

Quality assessment and certainty of evidence

According to the GRADE's approach, the certainty of the evidence was low, as all included studies had an observational design and the overall quality was fair to poor. Quality assessment of the individual studies measured by the NOS resulted in a fair quality score for 22 studies and a poor quality score for 7 studies (Additional file Table E).

Short-term survival

Meta-analysis showed no difference in short-term survival for VA-ECMO treated patients and control patients (RR 0.91, 95% CI 0.71–1.16) (Fig. 1). The average weighted short-term survival proportion of VA-ECMO treated acute PE patients was 0.81 (95% CI 0.59–0.97) in shock patients, 0.50 (95% CI 0.39–0.60) in cardiac arrest patients and 0.34 (95% CI 0.21–0.49) in ECPR patients (shown in Fig. 3). The individual study results on survival outcomes of VA-ECMO vs. control patients are summarised in Table 2. For the three VA-ECMO treated subgroups (i.e., shock, cardiac arrest, and ECPR) results are shown in Additional file Table F.

There was significant heterogeneity between the studies regarding short-term survival in shock patients and cardiac arrest patients. No significant risk of publication bias was found. Additional file Table G shows the assessment of heterogeneity and risk of publication bias for short-term survival of VA-ECMO vs. control patients and per subgroup. Additional file Appendix 2 shows the funnel and influence plot of short-term survival.

As mentioned, there were limited control groups available for the subgroup analysis. Only two studies reported VA-ECMO patients with a control group regarding survival outcomes in shock patients. Kjaergaard et al. [14] (N = 38) showed a survival rate of 81.8% in the control group and Takahashi et al. [16] (N = 24) showed a survival rate of 100% in the VA-ECMO treated group as well as the control group. For cardiac arrest three studies included a control group. Mandigers et al. [10] (N = 68) showed a survival rate of 31.8% in the VA-ECMO treated group and 10.9% in the control group. Kjaergaard et al. [14] (N = 38) showed a survival rate of 54.5% in the VA-ECMO treated group and 80%

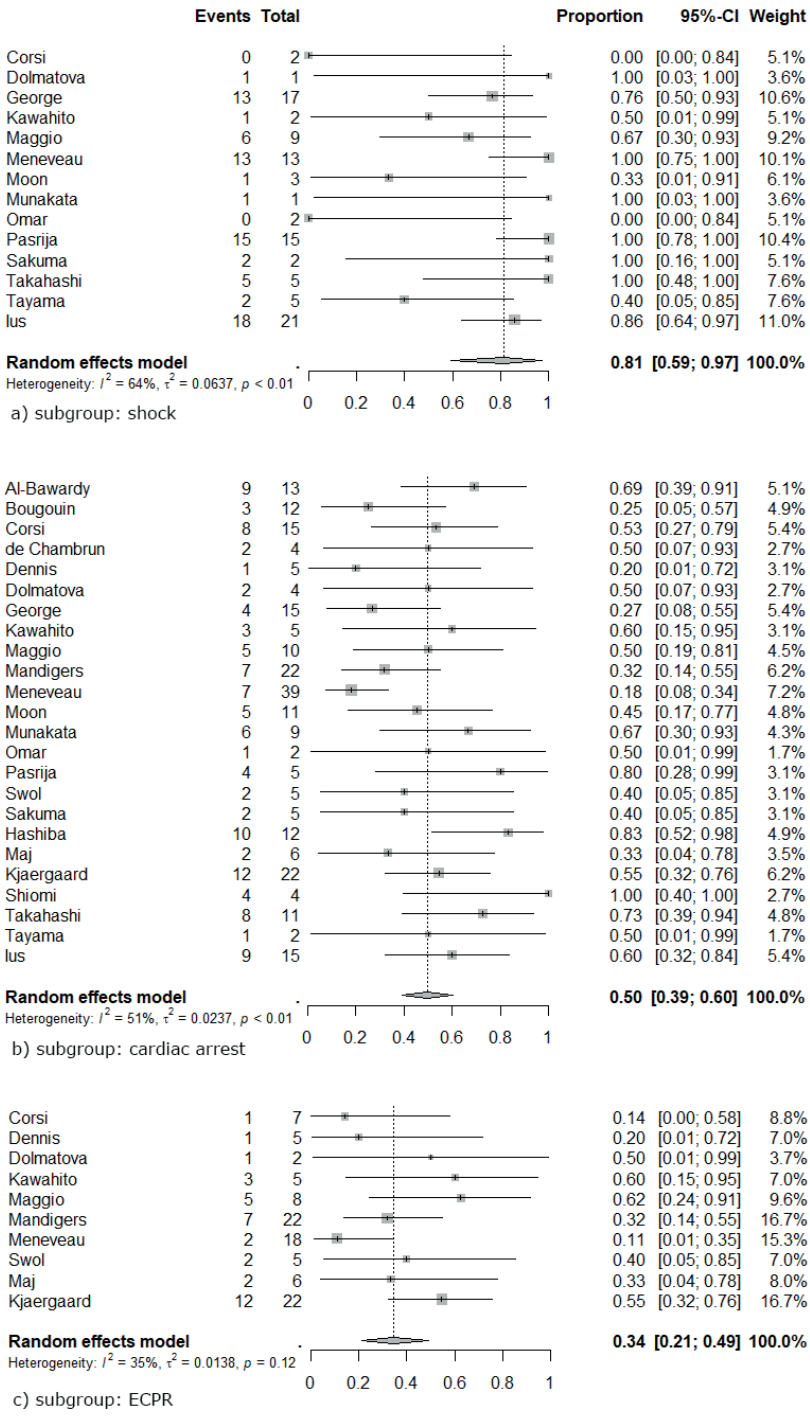


Figure 3 | Short-term survival of VA-ECMO patients per subgroup (shock, cardiac arrest and ECPR).

Table 2 | Survival outcomes of massive pulmonary embolism patients treated with/without VA-ECMO.

		Short-term survival (n, %)			Long-term survival (n, %)		
	Study	**Definition**	**VA-ECMO**	**Control**	**Definition**	**VA-ECMO**	**Control**
Studies including VA-ECMO and control patients							
3	Bougouin	hospital	3/12 (25.0)	16/70 (22.9)			
8	Funakoshi	30 day	60/112 (53.6)	177/249 (71.1)			
13	Mandigers	hospital	7/22 (31.8)	5/46 (10.9)			
14	Meneveau	30-day	20/52 (38.5)	73/128 (57.0)	90-day	18/52 (34.6)	68/128 (53.1)
15	Minakawa	hospital/ 30-day	71/94 (75.5)	211/261 (80.8)			
16	Moon	hospital	6/14 (42.8)	2/9 (22.2)	90-day	6/14 (42.9)	
24	Kjaergaard	30 day	12/22 (54.5)	13/16 (81.3)	1 year	10/22 (45.5)	9/13 (69.2)
25	Shiomi	hospital	9/9 (100.0)	18/22 (81.8)			
26	Takahashi	30 day	13/16 (81.3)	8/8 (100.0)			
Studies including only VA-ECMO patients, without control group							
1	Al-Bawardy	30 day	9/13 (69.2)		1 year	6/13 (46.2)	
2	Aso	hospital	127/353 (36.0)				
4	Corsi	hospital	8/17 (47.1)		90 day	8/17 (47.1)	
5	de Chambrun	hospital	2/4 (50.0)				
6	Dennis	hospital	1/5 (20.0)				
7	Dolmatova	hospital	3/5 (60.0)				
9	George	hospital	17/32 (53.1)				
10	Kawahito	hospital	4/7 (57.1)				
11	Maggio	hospital	11/19 (57.9)		1 year	11/19 (57.9)	
12	Malekan	hospital	4/4 (100.0)				
17	Munakata	30-day	7/10 (70.0)				
18	Omar	hospital	1/4 (25.0)				
19	Pasrija	hospital	19/20 (95.0)		90-day	19/20 (95.0)	
20	Swol	hospital	2/5 (40.0)				
21	Sakuma	hospital	4/7 (57.1)				
22	Hashiba	hospital	10/12 (83.3)				
23	Maj		2/6 (33.3)				
27	Tayama		3/7 (42.9)				
28	Ius	hospital	23/36 (63.9)				
29	Elbadawi	hospital	84/219 (38.4)				
Total			***341/785 = 43.4%***				

VA-ECMO = veno arterial extracorporeal membrane oxygenation, CPC = cerebral performance category

CPC 1/2 score of survivors		Causes of death	
VA-ECMO	Control	VA-ECMO	Control
		Neurologic n= 11 (50.0), hemodynamic n=2 (9.0),	Neurologic n=2 (4.3),
6/7 (86.0)	3/4 (75.0)	(multi)organ dysfunction syndrome n=2 (9.0)	hemodynamic n=39 (84.8)
		Hemodynamic n=3 (13.6)	Neurologic n=1 (6.3)
			Neurologic n=2 (22.2), (multi) organ dysfunction syndrome n=1 (4.5)
		Neurologic n=2 (12.5), (multi) organ dysfunction syndrome n=1 (6.25)	
2/2 (100.0)			
1/1 (100.0)			
		Neurologic n= 1 (20.0), hemodynamic n= 1 (20.0)	
		Hemodynamic n=2 (28.6)	
		Neurologic n=4 (21), hemodynamic n=1 (5.2), (multi) organ dysfunction syndrome n=1 (5.2)	
		(multi) organ dysfunction syndrome n=1 (25.0)	
19/19 (100.0)		Neurologic n=1 (5.0)	
		Neurologic n=1 (20), hemodynamic n=2 (40.0)	
7/10 (70.0)			
		Hemodynamic n=3 (42.9), (multi) organ dysfunction syndrome n=1 (14.3)	
		Neurologic n=7 (19.4), hemodynamic n=2 (5.6), (multi)organ dysfunction syndrome n=2 (5.6)	

in the control group. Shiomi et al. [15] (N = 31) showed a survival rate of 100% in the VA-ECMO treated group and 50% in the control group.

Factors associated with survival in patients with VA-ECMO

Of the 24 studies included in the meta-analysis on patients treated with VA-ECMO, 12 studies (n = 137) reported the age of individual patients, 16 studies (n = 239) reported sex differences, 22 studies (n = 330) reported cardiac arrest, 17 studies (n = 275) reported surgical embolectomy, 11 studies (n = 193) reported CDT, 15 studies (n = 225) reported systemic thrombolysis and 14 studies (n = 178) reported VA-ECMO as single treatment.

Two factors were associated with a significant difference in survival (Additional file Table H). Age > 60 years was associated with lower chance of survival, compared with age ≤ 60 years (RR 0.72, 95% CI 0.52–0.99). Surgical embolectomy was associated with higher chance of survival, compared with patients who did not undergo surgical embolectomy (RR 1.96, 95%CI 1.39–2.76). Also, there was a trend toward a lower survival for patients who suffered a cardiac arrest prior to or during VA-ECMO placement, compared to patients without cardiac arrest (RR 0.88, 95% CI 0.77–1.01). Male sex, catheter directed therapy, systemic thrombolysis and ECMO as single treatment were not associated with a difference in survival. Forest plots of the evaluated factors are included in the Additional file Appendix 3: A-G.

Assessment of the risk of publication bias showed no significant bias for the evaluated factors. Also, no significant heterogeneity was identified. The funnel plots are included in the Additional file Appendix 4: A-G and the influence plots are included in the Additional file Appendix 5: A-G. Sensitivity analyses of the results by exclusion of outlying studies did not result in a significant difference (Additional file Table I).

DISCUSSION

In this systematic review and meta-analysis, we found insufficient evidence of short-term survival benefit for VA-ECMO treatment in acute PE patients. Furthermore, in acute PE patients who were treated with VA-ECMO, we found that age ≤ 60 years and treatment with surgical embolectomy were associated with improved survival.

A possible explanation why VA-ECMO treatment did not improve short-term survival in acute PE patients might be that patients who needed VA-ECMO treatment may be more severely ill and hemodynamically compromised than patients without VA-ECMO treatment. Furthermore, VA-ECMO treatment is associated with severe complications, which may counterbalance a possible benefit of treatment.

In the broad continuum of obstructive shock, acute PE resulting in a cardiac arrest is the most severe form of shock which probably justifies VA-ECMO treatment. Even in

patients treated with ECPR, we found a short-term survival rate of 34%. This is higher than the survival rate of patients with cardiac arrest due to acute PE without VA-ECMO treatment ranging from 8.5–18.3% as reported in previous studies. [37,38]

In patients treated with VA-ECMO for acute PE, age ≤ 60 years and surgical embolectomy were associated with higher chance of survival. Furthermore, we found a trend ($p = 0.06$) toward lower survival in patients suffering a cardiac arrest before VA-ECMO treatment, compared to non-cardiac arrest patients. Most probably, this higher survival indicates that younger patients and patients who are in a condition good enough to undergo a surgical embolectomy, are the less ill patients with a higher a priori chance of survival. The trend toward lower survival in cardiac arrest patients could be explained by the severity of the illness as well as resuscitation difficulties, as conventional CPR is often insufficient in patients with massive PE due to a right ventricle outflow obstruction [[39], [40], [41]].

We performed a comprehensive systematic review evaluating survival in VA-ECMO treated and control acute PE patients. To our knowledge, this is the first meta-analysis to examine the survival for predefined subgroups and predictors for survival in acute PE patients with VA-ECMO treatment. A previous review published in 2015 evaluating the role of ECMO in acute PE included 78 patients treated with ECMO (11 case reports, 9 case series). [42] Although we included studies reporting on 4 patients or more, we were able to include 1138 patients treated with VA-ECMO in our review. The difference in sample size between our and the previous review highlights the fact that VA-ECMO is increasingly utilized as a treatment strategy in acute PE.

Despite the low evidence and lack of benefit of VA-ECMO treatment in the overall acute PE group, there may be a possible benefit in the subgroup of patients who suffered a (refractory) cardiac arrest. More research is needed to find out if VA-ECMO treatment could be beneficial. In severe shock patients as well as patients suffering (refractory) cardiac arrest it is important to perform prospective studies to compare VA-ECMO treated patients with non-VA-ECMO treated patients. Cardiac arrest with or without ROSC before ECMO placement are different entities which may have a very different prognosis. Unfortunately, most of the included articles did not differentiate between these subgroups or report separate outcome. Future studies should clearly differentiate between patients who had a cardiac arrest but gained ROSC before ECMO placement and patients with ECPR.

Additionally, the advantages or disadvantages of systemic thrombolysis in patients who are treated with VA-ECMO has to be investigated. Also, in order to adequately compare therapies and their outcome, studies should more clearly report the indication and timing of reperfusion therapies. For instance, the use of ECMO treatment prior to surgical intervention (and maintained during or removed after procedure) can have a different indication and outcome than ECMO treatment after surgical intervention.

Perfusion therapy with thrombolysis resulted in a reduction of adverse outcome (i.e. combined end-point of mortality and recurrent PE) in a population consisting mostly of high-risk PE patients with the presence of cardiogenic shock. [2] The risk of severe bleeding with this treatment is approximately 10%. However, if thrombolytic therapy is combined with ECMO there is an additional increased risk of bleeding (due to the need for vascular access) which should be taken into careful consideration. The use of ECMO alone as reperfusion method could offer an alternative, but is currently considered controversial. We speculate that in patients in whom ECMO treatment is deemed necessary a combination of ECMO and surgical intervention may be a better option than ECMO combined with thrombolysis. However, with the current data it is impossible to derive an evidence based recommendation regarding this subject.

Limitations

Only limited evidence can be derived from the present data due to the observational design of the included studies, only fair-poor quality of the individual studies, relatively small sample sizes and substantial heterogeneity between the studies regarding the primary outcome. Due to the observational nature of the studies there were discrepancies between ECMO and control patients which makes it difficult to interpret results. For example, the proportion of patients with cardiac arrest differed among ECMO and control patients in the studies performed by Funakoshi, Meneveau, Kjaergaard and Takahashi. Also, the indication for ECMO treatment differed among studies or was not reported.

Although we performed an extensive systematic review of the current available evidence regarding VA-ECMO treatment in acute PE, we applied study selection criteria (exclusion of studies published before the year 1980 and/or less than 4 patients and language restrictions [i.e., only English/Dutch]) which may limit our findings.

Another limitation is that we were unable to analyse the effect of complications in ECMO treated patients. ECMO is associated with several major adverse events such as bleeding and this should be properly investigated. However, due to heterogeneity among the included studies or the absence of classification of complications this analysis could not be performed in this meta-analysis.

CONCLUSIONS

At present, there is insufficient evidence that VA-ECMO treatment improves survival of acute PE patients. Low quality evidence suggest that VA-ECMO patients aged ≤60 years or who received SE have higher short-term survival rates. Considering the limited evi-

dence derived from the present data, this study emphasizes the need for prospective studies.

REFERENCES

1. Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. Secular Trends in Incidence and Mortality of Acute Venous Thromboembolism: The AB-VTE Population-Based Study. The American journal of medicine. 2016;129(8):879.e19-25.
2. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. Eur Heart J. 2019;40(42):3453-5.
3. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.
4. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet (London, England). 2002;359(9300):57-61.
5. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology. 2011;64(4):401-6.
6. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2009.
7. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. version 5.1 ed2011.
8. Bougouin W, Marijon E, Planquette B, Karam N, Dumas F, Celermajer DS, et al. Pulmonary embolism related sudden cardiac arrest admitted alive at hospital: Management and outcomes. Resuscitation. 2017;115:135-40.
9. Funakoshi H, Matsui H, Fushimi K, Yasunaga H. Variation in patient backgrounds, practice patterns, and outcomes of high-risk pulmonary embolism in Japan: A retrospective cohort study. 2018;59(2):367-71.
10. Mandigers L, Scholten E, Rietdijk WJR, den Uil CA, van Thiel RJ, Rigter S, et al. Survival and neurological outcome with extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest caused by massive pulmonary embolism: A two center observational study. Resuscitation. 2018;136:8-13.
11. Meneveau N, Guillon B, Planquette B, Piton G, Kimmoun A, Gaide-Chevronnay L, et al. Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases. Eur Heart J. 2018;39(47):4196-204.
12. Minakawa M, Fukuda I, Miyata H, Motomura N, Takamoto S, Taniguchi S, et al. Outcomes of Pulmonary Embolectomy for Acute Pulmonary Embolism. 2018;82(8):2184-90.
13. Moon D, Lee SN, Yoo KD, Jo MS. Extracorporeal membrane oxygenation improved survival in patients with massive pulmonary embolism. Ann Saudi Med. 2018;38(3):174-80.
14. Kjaergaard B, Kristensen JH, Sindby JE, de Neergaard S, Rasmussen BS. Extracorporeal membrane oxygenation in life-threatening massive pulmonary embolism. Perfusion. 2019;34(6):467-74.
15. Shiomi D, Kiyama H, Shimizu M, Yamada M, Shimada N, Takahashi A, et al. Surgical embolectomy for high-risk acute pulmonary embolism is standard therapy. Interact Cardiovasc Thorac Surg. 2017;25(2):297-301.
16. Takahashi H, Okada K, Matsumori M, Kano H, Kitagawa A, Okita Y. Aggressive surgical treatment of acute pulmonary embolism with circulatory collapse. Ann Thorac Surg. 2012;94(3):785-91.
17. Al-Bawardy R, Rosenfield K, Borges J, Young MN, Albaghdadi M, Rosovsky R, et al. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a case series and review of the literature. Perfusion (United Kingdom). 2019;34(1):22-8.

18. Aso S, Matsui H, Fushimi K, Yasunaga H. In-hospital mortality and successful weaning from venoarterial extracorporeal membrane oxygenation: analysis of 5,263 patients using a national inpatient database in Japan. Crit Care. 2016;20:80.
19. Corsi F, Lebreton G, Brechot N, Hekimian G, Nieszkowska A, Trouillet JL, et al. Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation. Crit Care. 2017;21(1):76.
20. De Chambrun MP, Brechot N, Hekimian G, Lebreton G, Schmidt M, Demondion P, et al. Veno-arterial ECMO for refractory cardiogenic shock following cardiac arrest. Annals of Intensive Care Conference: French Intensive Care Society, International Congress Reanimation. 2016;6(SUPPL. 1).
21. Dennis M, McCanny P, D'Souza M, Forrest P, Burns B, Lowe DA, et al. Extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest: A multicentre experience. International Journal of Cardiology. 2017;231:131-6.
22. Dolmatova EV, Moazzami K, Cocke TP, Elmann E, Vaidya P, Ng AF, et al. Extracorporeal Membrane Oxygenation in Massive Pulmonary Embolism. Heart Lung. 2017;46(2):106-9.
23. George B, Davis G, Guglin M, Smyth S. Reply to: A protocolized approach to veno-arterial extracorporeal membrane oxygenation for massive pulmonary embolism. Resuscitation. 2018;126:e13.
24. Kawahito K, Murata S, Adachi H, Ino T, Fuse K. Resuscitation and circulatory support using extracorporeal membrane oxygenation for fulminant pulmonary embolism. Artif Organs. 2000;24(6):427-30.
25. Maggio P, Hemmila M, Haft J, Bartlett R. Extracorporeal life support for massive pulmonary embolism. J Trauma. 2007;62(3):570-6.
26. Malekan R, Saunders PC, Yu CJ, Brown KA, Gass AL, Spielvogel D, et al. Peripheral extracorporeal membrane oxygenation: comprehensive therapy for high-risk massive pulmonary embolism. Ann Thorac Surg. 2012;94(1):104-8.
27. Munakata R, Yamamoto T, Hosokawa Y, Tokita Y, Akutsu K, Sato N, et al. Massive pulmonary embolism requiring extracorporeal life support treated with catheter-based interventions. Int Heart J. 2012;53(6):370-4.
28. Omar HR, Miller J, Mangar D, Camporesi EM. Experience with extracorporeal membrane oxygenation in massive and submassive pulmonary embolism in a tertiary care center. 2013;31(11):1616-7.
29. Pasrija C, Kronfli A, George P, Raithel M, Boulos F, Herr DL, et al. Utilization of Veno-Arterial Extracorporeal Membrane Oxygenation for Massive Pulmonary Embolism. Ann Thorac Surg. 2018;105(2):498-504.
30. Swol J, Buchwald D, Strauch J, Schildhauer TA. Extracorporeal life support (ECLS) for cardiopulmonary resuscitation (CPR) with pulmonary embolism in surgical patients - a case series. Perfusion. 2016;31(1):54-9.
31. Sakuma M, Nakamura M, Yamada N, Nakano T, Shirato K. Percutaneous cardiopulmonary support for the treatment of acute pulmonary embolism: summarized review of the literature in Japan including our own experience. Ann Vasc Dis. 2009;2(1):7-16.
32. Hashiba K, Okuda J, Maejima N, Iwahashi N, Tsukahara K, Tahara Y, et al. Percutaneous cardiopulmonary support in pulmonary embolism with cardiac arrest. Resuscitation. 2012;83(2):183-7.
33. Maj G, Melisurgo G, De Bonis M, Pappalardo F. ECLS management in pulmonary embolism with cardiac arrest: which strategy is better? Resuscitation. 2014;85(10):e175-6.

34. Tayama E, Takaseya T, Hiratsuka R, Akasu K, Teshima H, Hayashida N, et al. Percutaneous cardiopulmonary support for treatment of massive pulmonary embolism. Journal of Artificial Organs. 2002;5(4):228-32.
35. Ius F, Hoeper MM, Fegbeutel C, Kuhn C, Olsson K, Koigeldiyev N, et al. Extracorporeal membrane oxygenation and surgical embolectomy for high-risk pulmonary embolism. The European respiratory journal. 2019;53(4).
36. Elbadawi A, Mentias A, Elgendy IY, Mohamed AH, Syed MH, Ogunbayo GO, et al. National trends and outcomes for extra-corporeal membrane oxygenation use in high-risk pulmonary embolism. 2019;24(3):230-3.
37. Javaudin F, Lascarrou JB, Le Bastard Q, Bourry Q, Latour C, De Carvalho H, et al. Thrombolysis During Resuscitation for Out-of-Hospital Cardiac Arrest Caused by Pulmonary Embolism Increases 30-Day Survival: Findings From the French National Cardiac Arrest Registry. Chest. 2019;156(6):1167-75.
38. Er F, Nia AM, Gassanov N, Caglayan E, Erdmann E, Hoppe UC. Impact of rescue-thrombolysis during cardiopulmonary resuscitation in patients with pulmonary embolism. PLoS One. 2009;4(12):e8323.
39. Logan JK, Pantle H, Huiras P, Bessman E, Bright L. Evidence-based diagnosis and thrombolytic treatment of cardiac arrest or periarrest due to suspected pulmonary embolism. Am J Emerg Med. 2014;32(7):789-96.
40. Kurkciyan I, Meron G, Sterz F, Janata K, Domanovits H, Holzer M, et al. Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. Arch Intern Med. 2000;160(10):1529-35.
41. Yousuf T, Brinton T, Ahmed K, Iskander J, Woznicka D, Kramer J, et al. Tissue Plasminogen Activator Use in Cardiac Arrest Secondary to Fulminant Pulmonary Embolism. Journal of clinical medicine research. 2016;8(3):190-5.

ADDITIONAL FILES

Table of contents

Appendix 1: search string PubMed, Embase and Cochrane Library, searched on 5-8-2019.

PubMed/Medline:

("Extracorporeal Membrane Oxygenation"[Mesh] OR extracorporeal membrane oxygenation*[tiab] OR extracorporeal oxygenation*[tiab] OR extracorporeal pump oxygenation*[tiab] OR extrapulmonary oxygenation*[tiab] OR extra-corporeal membrane oxygenation*[tiab] OR extra-corporeal oxygenation*[tiab] OR extra-corporeal pump oxygenation*[tiab] OR extra-pulmonary oxygenation*[tiab] OR ECMO[tiab] OR extracorporeal life support*[tiab] OR extra-corporeal life support*[tiab] OR ECLS[tiab] OR extracorporeal cardiopulmonary resuscitat*[tiab] OR extra-corporeal cardiopulmonary resuscitat*[tiab])

AND

("Pulmonary Embolism"[Mesh] OR pulmonary embol*[tiab] OR pulmonary thromboembol*[tiab] OR lung embol*[tiab] OR lung thromboembol*[tiab] OR pulmonary thrombo-embol*[tiab] OR lung embol*[tiab] OR lung thrombo-embol*[tiab])

EMBASE (OVID):

Database(s): Embase Classic+Embase
Search Strategy:

#	Searches
1	extracorporeal oxygenation/
2	(extracorporeal membrane oxygenation* or extracorporeal oxygenation* or extracorporeal pump oxygenation* or extrapulmonary oxygenation* or extra-corporeal membrane oxygenation* or extra-corporeal oxygenation* or extra-corporeal pump oxygenation* or extra-pulmonary oxygenation* or ECMO or extracorporeal life support* or extra-corporeal life support* or ECLS or extracorporeal cardiopulmonary resuscitat* or extra-corporeal cardiopulmonary resuscitat*).ti,ab,kw.
3	1 or 2
4	lung embolism/
5	(pulmonary embol* or pulmonary thromboembol* or lung embol* or lung thromboembol* or pulmonary thrombo-embol* or lung embol* or lung thrombo-embol*).ti,ab,kw.
6	4 or 5
7	3 and 6
8	limit 7 to dd=20190301-20190805

CENTRAL

ID Search Hits

#1 MeSH descriptor: [Extracorporeal Membrane Oxygenation] explode all trees

#2 (extracorporeal membrane oxygenation* or extracorporeal oxygenation* or extracorporeal pump oxygenation* or extrapulmonary oxygenation* or extra-corporeal membrane oxygenation* or extra-corporeal oxygenation* or extra-corporeal pump oxygenation* or extra-pulmonary oxygenation* or ECMO or extracorporeal life support* or extra-corporeal life support* or ECLS or extracorporeal cardiopulmonary resuscitat* or extra-corporeal cardiopulmonary resuscitat* or percutaneous cardiopulmonary support):ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Pulmonary Embolism] explode all trees

#5 (pulmonary embol* or pulmonary thromboembol* or lung embol* or lung thromboembol* or pulmonary thrombo-embol* or lung embol* or lung thrombo-embol*):ti,ab,kw (Word variations have been searched)

#6 #4 or #5

#7 #3 and #6 with Cochrane Library publication date Between Mar 2019 and Aug 2019

Table A | Criteria and indication for the decision to initiate VA-ECMO in the included studies.

	Study	Criteria/indication for ECMO initiation
1	Al-Bawardy	
2	Aso	
3	Bougouin	
4	Corsi	Acute refractory cardiovascular failure (defined as evidence of tissue hypoxia concomitant with adequate intravascular volume status); severely diminished RV or LVEF; low cardiac index (<2.0); sustained hypotension despite high-dose catecholamine infusion. Exclusion malignancies with fatal prognosis within 5 years or irreversible neurological pathologies and decisions to limit therapeutic interventions
5	de Chambrun	Persistence or aggravation of tissue hypoxia despite adequate fluid loading; severely depressed LVEF (<25%) with low cardiac output. Exclusion ECMO for refractory cardiac arrest under CPR
6	Dennis	Patients with refractory cardiac arrest without return of spontaneous circulation. ECMO for shock, following ROSC excluded
7	Dolmatova	
8	Funakoshi	
9	George	
10	Kawahito	Circulatory collapse being refractory to conventional treatment
11	Maggio	Profound shock despite and after optimal pharmacologic treatment. Exclusion age >70, irreversible neurologic injury, mechanical ventilation >7 days, and coexisting incurable illness
12	Malekan	Submassive PE patients deemed high risk for surgery
13	Mandigers	ECPR criteria: witnessed CA (last seen <5min) in patients <70 years with good quality of BLS/ALS (leading to an end-tidal CO2 >10mmHg) during at least 15 min and a low flow time <60 min.
14	Meneveau	
15	Minakawa	
16	Moon	Acute refractory cardiac failure: defined as evidence of tissue hypoxia concomitant with adequate intravascular volume status), severely diminished RV/LVEF, low cardiac index, and sustained hypotension despite high -dose catecholamine infusion
17	Munakata	Refractory shock or cardiac arrest
18	Omar	ECMO implemented as last resort for PE patients otherwise expected to die
19	Pasrija	Patients with a massive PE resulting in end-organ dysfunction or unclear neurologic status
20	Swol	In-hospital witnessed cardiac arrest and pulmonary embolism (ECLS implantation exclusively in critical, life-threatening situations)
21	Sakuma	
22	Hashiba	Witnessed cardiac arrest after emergency medical team contact or hospital survival.
23	Maj	
24	Kjaergaard	
25	Shiomi	Patients with preoperative cardiopulmonary arrest or those who were hemodynamically unstable and requiring a large amount of inotropes

Table A | Criteria and indication for the decision to initiate VA-ECMO in the included studies. (*continued*)

	Study	Criteria/indication for ECMO initiation
26	Takahashi	Experience with some patients in pre-shock with intermediate-risk PE falling further into shock at the start of anesthesia, or patients with floating thrombus in the right atrium who were already in cardiac arrest
27	Tayama	If acute circulatory failure could not be relieved by conventional therapy
28	Ius	Patients who remained in shock or under CPR despite supportive measures
29	Elbadawi	

Table B | Summary of included studies on VA-ECMO treatment in massive pulmonary embolism.

	Study	Year	Study design	Years of inclusion	Single- or Multicenter	Country	Total N=	Included patient population
Studies including VA-ECMO and control patients								
3	Bougouin	2017	descriptive	2011-2015	multi	France	82	PE patients with sudden cardiac arrest
8	Funakoshi	2018	cohort	2010-2014	multi	Japan	361	PE patients who received noradranaline within 1 day after admission and thrombolysis/surgical embolectomy within 1 day after admission
13	Mandigers	2018	cohort	2012-2017	multi	the Netherlands	68	ECPR patients
14	Meneveau	2018	cohort	2014-2015	multi	France	180	high risk PE
15	Minakawa	2018	cohort	2008-2014	multi	Japan	355	Patients who underwent pulmonary embolectomy
16	Moon	2018	cohort	2004-2017	single	Korea	23	Patients with confirmed massive PE with profound shock or in need of CPR
24	Kjaergaard	2019	cohort	2014-2017	single	Denmark	38	Massive PE with indication for ECMO
25	Shiomi	2017	cohort	2004-2014	single	Japan	31	Massive PE patients receiving surgical embolectomy
26	Takahashi	2012	cohort	2000-2011	single	Japan	24	Massive PE patients receiving surgical embolectomy
							1162	
Studies including only VA-ECMO patients, without control group								
1	Al-Bawardy	2019	descriptive	since 2012	single	USA	13	ECMO patients treated by PERT with suspicion of PE, and PE not ruled out after diagnostic testing
2	Aso	2016	descriptive	2010-2013	multi	Japan	5263	all VA-ECMO patients
4	Corsi	2017	descriptive	2006-2015	single	France	17	ECMO for suspected or confirmed massive PE
5	de Chambrun	2016	descriptive	2007-2015	single	France	94	VA-ECMO patients for refractory shock post cardiac arrest resuscitation
6	Dennis	2017	descriptive	2009-2016	multi	Australia	37	ECPR patients
7	Dolmatova	2017	descriptive	2011-2015	single	USA	50	PE patients were selected out of ECMO patients
9	George	2018	descriptive	2012-2015	single	USA	32	ECMO database in which patients with confirmed high-risk PE were selected
10	Kawahito	2000	descriptive	1994-1998	single	Japan	7	ECMO in fulmonant PE patients
11	Maggio	2007	descriptive	1992-2005	single	USA	21	Massive PE patients which were treated with ECMO

Table B | Summary of included studies on VA-ECMO treatment in massive pulmonary embolism. (*continued*)

Studies including VA-ECMO and control patients								
12	Malekan	2012	descriptive	2005-2011	single	USA	29	Submassive and massive PE patients, ECMO patients selected from this group
17	Munakata	2012	descriptive	1992-2008	single	Japan	35	Massive PE patients, of which ECLS treated patients included
18	Omar	2013	descriptive	2007-2011	single	USA	4	ECMO patients, of which PE patients were selected
19	Pasrija	2018	descriptive	2014-2016	single	USA	20	VA ECMO patients as initial intervention for massive PE
20	Swol	2016	descriptive	2018-2014	single	Germany	5	IHCA patients with PE
21	Sakuma	2009	descriptive		single	Japan	7	
22	Hashiba	2012	cohort	1998-2010	single	Japan	28	OHCA patients with massive PE treated with ECMO
23	Maj	2014	descriptive		single	Italy	6	Witnessed refractory cardiac arrest due to suspected pulmonary embolism
27	Tayama	2002	descriptive	1990-2001	single	Japan	7	Massive PE patients with indication for surgical embolectomy
28	Ius	2019	descriptive	2012-2018	single	Germany	36	High risk PE treated with ECMO
29	Elbadawi	2019	descriptive	2005-2013	multi	USA	219	Hospitalisations for PE, selected patients with ECMO
							5930	
Total							**7092**	

ECMO = extracorporeal membrane oxygenation, PERT = pulmonary embolism response team, PE = pulmonary embolism, VA-ECMO = veno arterial ECMO, ECPR = extracorporeal cardiopulmonary resuscitation, CPR = cardiopulmonary resuscitation

ECLS = extracorporeal life support, IHCA = in hospital cardiac arrest, OHCA = out of hospital cardiac arrest

Table C | Baseline characteristics of massive pulmonary embolism patients treated with/without VA-ECMO.

Studies including VA-ECMO and control patients									
		Number of PE patients		**Age (years)**		**Male (%)**		**Predisposing factors for PE**	
	Study	**VA-ECMO**	**Control**	**VA-ECMO**	**Control**	**VA-ECMO**	**Control**	**VA-ECMO**	**Control**
3	Bougouin	12	70					Postoperative n=4, immobilisation (incl fracture) n=4, hormonal use n=1, recent thrombosis/ history n=3	
8	Funakoshi	112	249	58,5 (16.2)	65.9 (14.8)	42 (38)	94 (38)	Malignancy n=4, recent thrombosis/ history n=3	
13	Mandigers	22	46	40 (IQR 30-59)	57 (51-63)	9 (41)	23 (51)	Postoperative n=10, immobilisation (incl fracture) n=25, malignancy n=4, hormonal use n=6, recent thrombosis/history n=17	
14	Meneveau	52	128	48 (15)	64 (15)	27 (52)	69 (54)		
15	Minakawa	94	261					Postoperative n=3, immobilisation (incl fracture) n=5	Postoperative n=6, immobilisation (incl fracture) n=3, malignancy n=2, recent thrombosis/ history n=1
16	Moon	14	9	54 (18)	65 (15)	4 (29)	0 (0)		
24	Kjaergaard	22	16	54 (IQR 47.75-67.75)	62 (45.25-69)	10 (45)	8 (50)		
25	Shiomi	9	22					Postoperative n=6, immobilisation (incl fracture) n=6, malignancy n=1, none n=2	Postoperative n=2, immobilisation (incl fracture) n=1, malignancy n=1, recent thrombosis/ history n=1, none n=2

Table C | Baseline characteristics of massive pulmonary embolism patients treated with/without VA-ECMO. (*continued*)

Studies including VA-ECMO and control patients								
26	Takahashi	16	8	58 (IQR 42.75-70)	69 (67.25-76)	4 (25)	3 (38)	Postoperative n=4, recent thrombosis/ history n=1
		353	***809***					

Studies including only VA-ECMO patients, without control group					
		Number of PE patients	**Age (years)**	**Male (%)**	**Predisposing factors for PE**
	Study	**VA-ECMO**	**VA-ECMO**	**VA-ECMO**	**VA-ECMO**
1	Al-Bawardy	13	49 (19)	7 (54)	Immobilisation (incl fracture) n=8, malignancy n=2, hormonal use n=3, recent thrombosis/ history n=4
2	Aso	353	60.6 (15.6)	131 (37)	
4	Corsi	17	51 (range: 18-70)	6 (35)	
5	de Chambrun	4			
6	Dennis	5			Immobilisation (incl fracture) n=1, malignancy n=1
7	Dolmatova	5	52 (11.5)	3 (60)	
9	George	32	56	17 (53)	Postoperative n=1, malignancy n=1, recent thrombosis/history n=2
10	Kawahito	7	61 (16)	2 (29)	Immobilisation (incl fracture) n=11, recent thrombosis/history n=2
11	Maggio	19	41 (13.8)	9 (47)	Malignancy n=1, recent thrombosis/ history n=1
12	Malekan	4	46 (20.6)	1 (25)	

Table C | Baseline characteristics of massive pulmonary embolism patients treated with/without VA-ECMO. (*continued*)

Studies including VA-ECMO and control patients					
17	Munakata	10	61 (IQR 32.75-75.75)	2 (20)	Postoperative n=1, immobilisation (incl fracture) n=1, malignancy n=1
18	Omar	4	49 (IQR 39.8-56.5)	2 (50)	Postoperative n=7, immobilisation (incl fracture) n=12, malignancy n=1, recent thrombosis/history n=14
19	Pasrija	20	47 (IQR 32-59)	9 (45)	Postoperative n=1, immobilisation (incl fracture) n=3
20	Swol	5	45 (IQR 39.5-51.5)	4 (80)	Postoperative n=2, immobilisation (incl fracture) n=2, none n=2
21	Sakuma	7	64 (IQR 37-75)	1 (14)	
22	Hashiba	12	65 (15.7)	4 (33)	
23	Maj	6			Postoperative n=4, immobilisation (incl fracture) n=3, malignancy n=2, none n=7
27	Tayama	7	62 (IQR 60-71)	1 (14)	
28	Ius	36	56 (range: 18-79)	23 (64)	
29	Elbadawi	219	42 (17.9)	148 (67.6)	
		785			
Total		**1138**	**809**		

mean +/- SD of median [IQR] SD = standard deviation, IQR = interquartile range, VA-ECMO = veno arterial extracorporeal membrane oxygenation, PE = pulmonary embolism

Table D | Classification of complications

#	Author	Complication bleeding	Other complications
1	Al-Bawardy	Major bleeding complications, based on International Society on Thrombosis and Hemostasis (ISTH) criteria, and characterized by bleeding location.	Residual heart strain (defined as an echocardiogram showing right ventricular dilatation, hypokinesis or elevated right ventricular systolic pressure or computed tomography (CT) showing right ventricle to left ventrical ratio >1), persistent symptoms on follow-up, chronic venous insufficiency and chronic thromboembolic pulmonary hypertension diagnosed by a physician during clinical follow up.
4	Corsi	Bleeding complications were reported using the Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO) classification.	In-ICU complications, e.g. arterial ischemia, surgical wound infection, stroke, and renal replacement therapy requirement, were recorded.
7	Dolmatova	Not reported	No definition, only descriptive.
9	George	No definition, only descriptive.	Not reported
11	Maggio	No definition, only descriptive.	No definition, only descriptive.
12	Malekan	No definition, only descriptive.	Not reported
13	Mandigers	Major bleeding in need of transfusion/ intervention or major bleeding limiting the treatment options such as thrombolysis or continuing of CPR	Cerebral haemorrhage; vascular/ischemic limb complications; infection [defined as any infection with positive culture in general, during admission for the CCPR group and during ECMO for the ECPR group]
14	Meneveau	Major and non-major bleeding complications, using the International Society on Thrombosis and Haemostasis (ISTH) definition.	Occurrence of stroke, need for renal replacement therapy, catheter site infection, ventilator-associated pneumonia, septicaemia, or multi-organ failure.
17	Munakata	No definition, only descriptive.	No definition, only descriptive.
19	Pasrija	Including bleeding that required blood product transfusion on ECMO.	AKI that required RRT, new hemodialysis at discharge, sepsis, tracheostomy, RV disfunction at discharge, and ECMO-related complications (incl bleeding), stroke after cannulation, and vascular complications related to ECMO
20	Swol	No definition, only descriptive.	No definition, only descriptive.
22	Hashiba	No definition, only descriptive.	Not reported
23	Maj	No definition, only descriptive.	No definition, only descriptive.
24	Kjaergaard	No definition, only descriptive.	No definition, only descriptive.
26	Takahashi	No definition, only descriptive.	No definition, only descriptive.
27	Tayama	No definition, only descriptive.	No definition, only descriptive.
28	Ius	No definition, only descriptive.	No definition, only descriptive.
29	Elbadawi	No definition, only descriptive.	No definition, only descriptive.

Table E | Modified Newcastle-Ottawa Quality assessment scale; based on primary outcome measure survival.

		Selection (4)				Comparability (2)		Outcome (3)			☆		
	Study	1. Representativeness of exposed cohort	2. Study population clearly defined	3. Exposed and non-exposed cohort selected from same cohort	4. Definition and selection of the non-exposed cohort	5. Study adjusted for **cardiac arrest and shock**	6. Study propensity matched cohorts	7. Follow-up long enough for outcome to occur (>30 days)	8. Survival outcomes described	9. Adequacy of follow up (>80% FU of cohort(s))		**Overall score (max. 9)**	**Overall score (quality)**
1	Al-Bawardy	☆	☆					☆		☆		4	fair
2	Aso									☆		1	poor
3	Bougouin	☆	☆	☆						☆		4	fair
4	Corsi	☆						☆	☆	☆		4	fair
5	de Chambrun	☆						☆	☆	☆		4	fair
6	Dennis	☆							☆	☆		3	poor
7	Dolmatova	☆	☆						☆	☆		4	fair
8	Funakoshi			☆	☆			☆		☆		4	fair
9	George	☆	☆							☆		3	poor
10	Kawahito	☆	☆						☆	☆		4	fair
11	Maggio	☆	☆					☆	☆	☆		5	fair
12	Malekan	☆	☆					☆		☆		4	fair
13	Mandigers	☆		☆	☆			☆	☆	☆		6	fair
14	Meneveau	☆		☆		☆		☆	☆	☆		5	fair
15	Minakawa	☆		☆				☆		☆		4	fair
16	Moon	☆	☆		☆			☆		☆		5	fair
17	Munakata	☆	☆					☆	☆	☆		5	fair
18	Omar	☆	☆						☆	☆		4	fair
19	Pasrija	☆	☆					☆	☆	☆		5	fair
20	Swol	☆							☆	☆		3	fair
21	Sakuma	☆								☆		2	poor
22	Hashiba	☆	☆						☆	☆		4	fair
23	Maj	☆								☆		2	poor
24	Kjaergaard	☆						☆	☆	☆		4	fair
25	Shiomi	☆		☆				☆	☆	☆		5	fair
26	Takahashi	☆	☆	☆				☆	☆	☆		6	fair
27	Tayama	☆							☆	☆		3	poor
28	Ius	☆	☆						☆	☆		4	fair
29	Elbadawi											0	poor

Table F | Survival outcomes of massive PE patients treated with VA-ECMO, divided by shock, cardiac arrest, and ECPR

		Short-term survival ECMO patients (n, %)				Short-term survival control patients (n, %)		
	Study	Definition	Shock patients	Cardiac arrest patients		Definition	Shock patients	Cardiac arrest patients
				VA-ECMO after ROSC	*ECPR*			
1	Al-Bawardy	30 day	0/0 (0.0)	9/13 (69.2)		30 day		
3	Bougouin	hospital	0/0 (0.0)	3/12 (25.0)		hospital		
4	Corsi	hospital	0/2 (0.0)	8/15 (53.3)	1/7 (14.3)	hospital		
5	de Chambrun	hospital	0/0 (0.0)	2/4 (50.0)		hospital		
6	Dennis	hospital	0/0 (0.0)		1/5 (20.0)	hospital		
7	Dolmatova	hospital	1/1 (100.0)	2/4 (50.0)	1/2 (50.0)	hospital		
9	George	hospital	13/17 (76.5)	4/15 (26.7)		hospital		
10	Kawahito	hospital	1/2 (50.0)		3/5 (60.0)	hospital		
11	Maggio	hospital	6/9 (66.7)	5/10 (50.0)	5/8 (62.5)	hospital		
13	Mandigers	hospital	0/0 (0.0)		7/22 (31.8)	hospital	0/0 (0.0)	5/46 (10.9)
14	Meneveau	30-day	13/13 (100.0)	7/39(17.9)	2/18 (11.1)	30-day		
16	Moon	hospital	1/3 (33.3)	5/11 (45.5)		hospital		
17	Munakata	30-day	1/1 (100.0)	6/9 (66.7)		30-day		
18	Omar	hospital	0/2 (0.0)	1/2 (50.0)		hospital		
19	Pasrija	hospital	15/15 (100.0)	4/5 (80.0)		hospital		
20	Swol	hospital	0/0 (0.0)		2/5 (40.0)	hospital		
21	Sakuma	hospital	2/2 (100.0)	2/5 (40.0)		hospital		
22	Hashiba	hospital	0/0 (0.0)	10/12 (83.3)		hospital		
23	Maj		0/0 (0.0)		2/6 (33.3)			
24	Kjaergaard	30 day	0/0 (0.0)		12/22 (54.5)	30 day	9/11 (81.8)	4/5 (80.0)
25	Shiomi	hospital		4/4 (100.0)		hospital		2/4 (50.0)
26	Takahashi	30 day	5/5 (100.0)	8/11 (72.7)		30 day	8/8 (100.0)	0/0 (0.0)
27	Tayama		2/5 (40.0)	1/2 (50.0)				
28	Ius	hospital	18/21 (85.7)	9/15 (60.0)		hospital		

VA-ECMO = veno arterial extracorporeal membrane oxygenation, CPC = cerebral performance category

CPC 1/2 score of survivors			Causes of death	
Shock patients	Cardiac arrest patients		VA-ECMO	Control
	VA-ECMO after ROSC	*ECPR*		
0/0 (0.0)	2/2 (100.0)			
0/0 (0.0)	1/1 (100.0)	1/1 (100.0)		
			Neurologic n= 1 (20.0), hemodynamic n= 1 (20.0)	
			Hemodynamic n=2 (28.6)	
			Neurologic n=4 (21.0), hemodynamic n=1 (5.2), (multi) organ dysfunction syndrome n=1 (5.2)	
	6/7 (86.0)	6/7 (86.0)	Neurologic n= 11 (50.0), hemodynamic n=2 (9.0), (multi)organ dysfunction syndrome n=2 (9.0)	Neurologic n=2 (4.3), hemodynamic n=39 (84.8)
			(multi) organ dysfunction syndrome n=1 (25.0)	
15/15 (100.0)	4/4 (100.0)		Neurologic n=1 (5.0)	
			Neurologic n=1 (20.0), hemodynamic n=2 (40.0)	
0/0(0.0)	7/10 (70.0)			
			Hemodynamic n=3 (13.6)	Neurologic n=1 (6.3)
				Neurologic n=2 (22.2), (multi) organ dysfunction syndrome n=1 (4.5)
			Neurologic n=2 (12.5), (multi) organ dysfunction syndrome n=1 (6.25)	
			Hemodynamic n=3 (42.9), (multi) organ dysfunction syndrome n=1 (14.3)	
12/18 (66.7)	5/9 (55.6)		Neurologic n=7 (19.4), hemodynamic n=2 (5.6), (multi)organ dysfunction syndrome n=2 (5.6)	

Table G | Meta-analysis; short-term survival in PE patients treated with and without VA-ECMO; and short-term survival per subcategory for only VA-ECMO treated patients (risk ratio, heterogeneity and publication bias)

				Heterogeneity (%)			Publication bias
	No of studies	Total no of patients	RR (95% CI; p-value) or Weighted Proportion (WP, 95% CI)	I2	Tau2	p-value	Egger regression*
Short-term survival	9	1152	RR 0.91 (0.71-1.16, 0.40)	**69**	0.04	**<0.01**	0.15
Per subcategory							
Shock	14	98	WP 0.81 (0.59-0.91)	**64**	0.06	**<0.01**	
Cardiac arrest	24	253	WP 0.50 (0.39-0.60)	**51**	0.02	**<0.01**	
ECPR	10	100	WP 0.34 (0.21-0.49)	35	0.01	0.12	

RR = risk ratio, 95% CI = 95% confidence intervals, bold values are significant at 5% alpha level. ECPR = Extracorporeal cardiopulmonary resuscitation

Pooled risk ratios/proportions are calculated on the basis of random effects models

* Eggers regression is the p-value of the bias estimate, where p<0.10 show significant publication bias, NA as for two samples are not enough to estimate publication bias

Table H | Meta-analysis; survival in PE patients treated with VA-ECMO, risk ratio, heterogeneity and publication bias

				Heterogeneity (%)			Publication bias
	No of studies	Total no of patients	RR (95% CI; p-value)	I2	Tau2	p-value	Egger regression*
Age > 60 years	12	137	**0.72 (0.52-0.99, <0.05)**	0	0	0.89	0.53
Male	16	239	0.88 (0.69-1.12, 0.27)	0	0	0.75	0.78
Cardiac arrest	22	330	0.88 (0.77-1.01, 0.06)	31.2	0.02	0.08	0.92
Surgical embolectomy	17	275	**1.96 (1.39-2.76, <0.01)**	0	0	0.76	0.63
CDT	11	193	1.07 (0.70-1.63, 0.73)	27.9	0.15	0.19	0.61
Systemic thrombolysis	15	225	0.85 (0.67-1.08, 0.17)	19.4	0.04	0.24	0.26
VA-ECMO alone	14	178	0.93 (0.65-1.34, 0.67)	0	0	0.56	0.89

RR = risk ratio, 95% CI = 95% confidence intervals, bold values are significant at 5% alpha level.

CDT = catheter directed thrombolysis/thrombectomy,VA-ECMO = veno arterial extracorporeal membrane oxygenation

Pooled risk ratios are calculated on the basis of random effects models.

* Eggers regression is the p-value of the bias estimate, where p<0.10 show significant publication bias, NA as for two samples are not enough to estimate publication bias.

Table I | Sensitivity analysis; Short-term survival and predictors for survival in PE patients treated with VA-ECMO, risk ratio, heterogeneity and publication bias

				Heterogeneity (%)			Publication bias
	No of studies	Total no of patients	RR (95% CI; p-value)	I2	Tau2	p-value	Egger regression*
Short-term survival	8	801	0.94 (0.71-1.25, 0.62)	**65**	0.04	**<0.01**	0.31
Age > 60 years	11	121	**0.69 (0.50-0.96, 0.03)**	0	0	0.89	0.42
Cardiac arrest	21	318	0.87 (0.75-1.00, 0.06)	36	0.03	0.05	0.74
Surgical embolectomy	15	219	**1.80 (1.30-2.49, <0.01)**	0	0	0.85	0.21
CDT	10	161	0.87 (0.72-1.06, 0.14)	0	0	0.90	0.92
VA-ECMO alone	13	174	0.93 (0.65-1.34, 0.67)	0	0	0.56	0.53

RR = risk ratio, 95% CI = 95% confidence intervals, bold values are significant at 5% alpha level

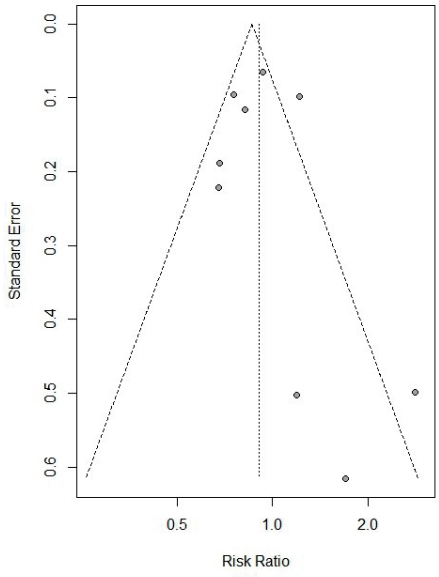
CDT = catheter directed thrombolysis/thrombectomy,VA-ECMO = veno arterial extracorporeal membrane oxygenation

Pooled risk ratios are calculated on the basis of random effects models.

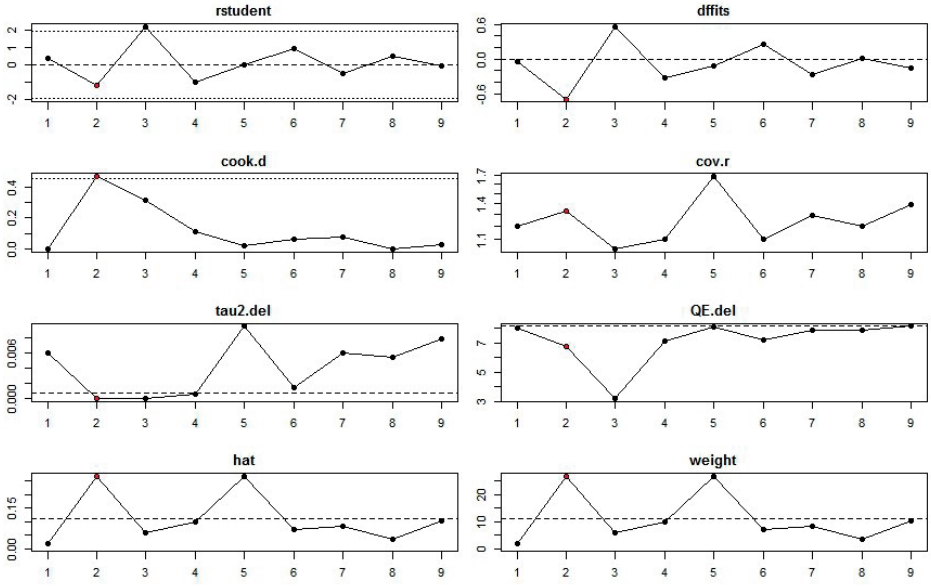
* Eggers regression is the p-value of the bias estimate, where p<0.10 show significant publication bias, NA as for two samples are not enough to estimate publication bias.

Appendix 2 | Plots of short-term survival

A) Funnel plot

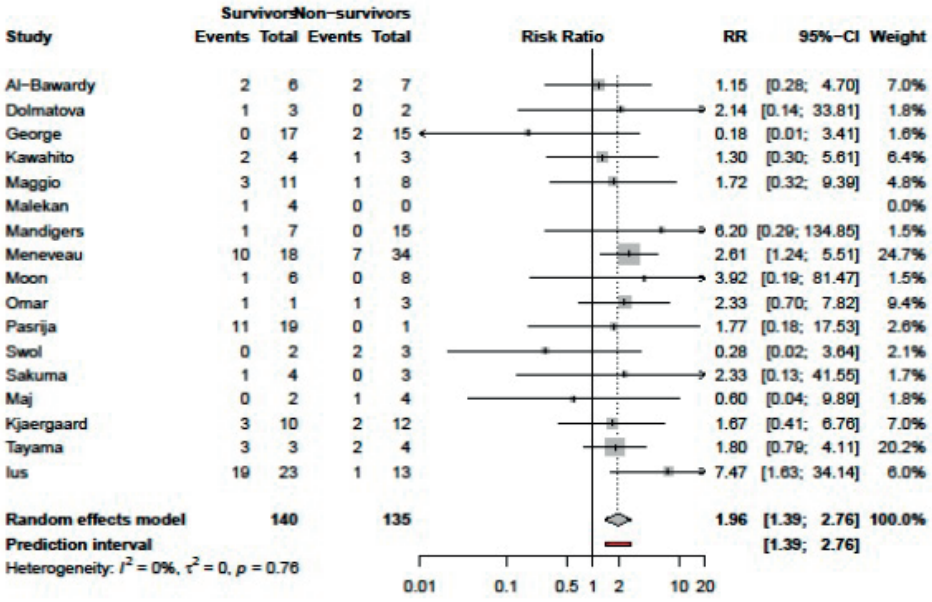


B) Influence plot

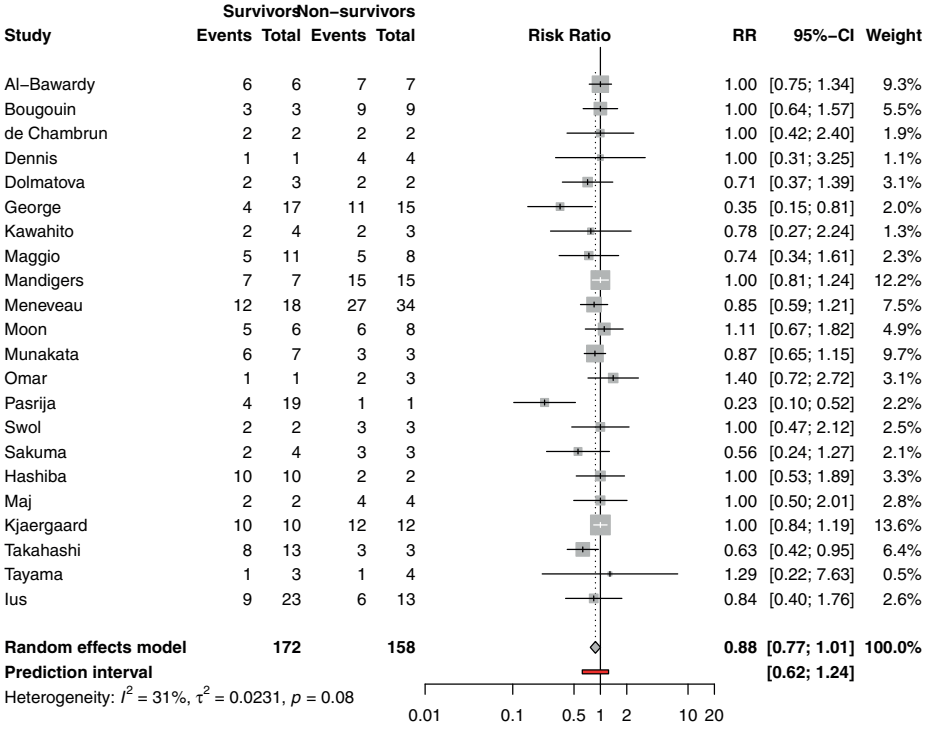


Appendix 3 | Forest plots of evaluated factors.

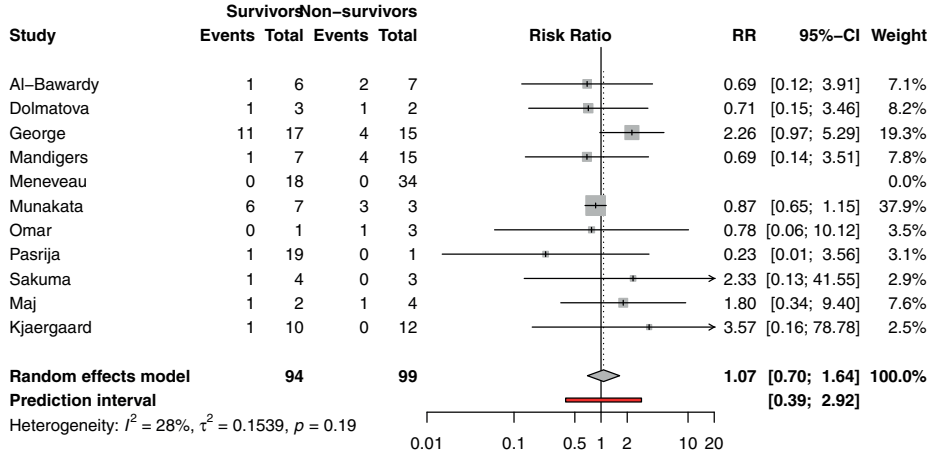
A) Age



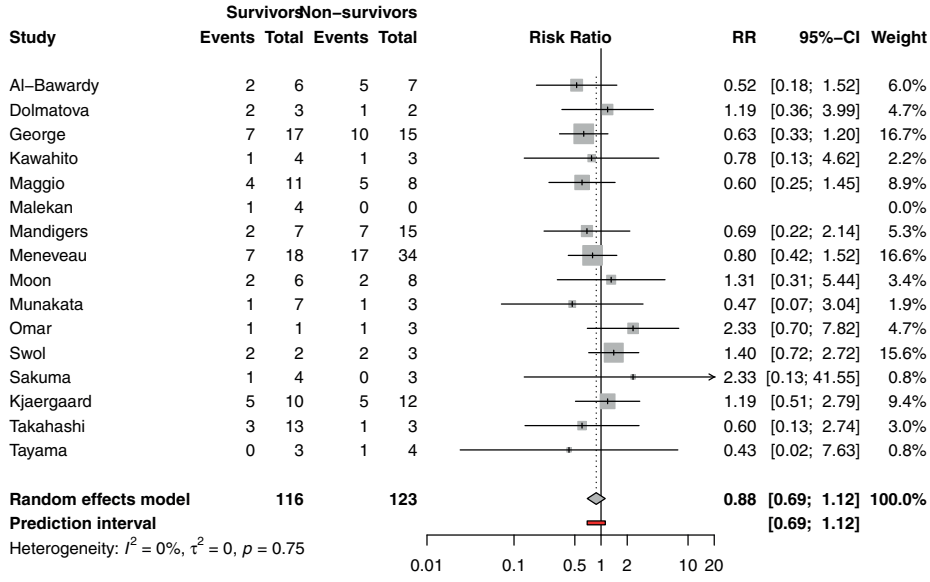
B) Cardiac arrest



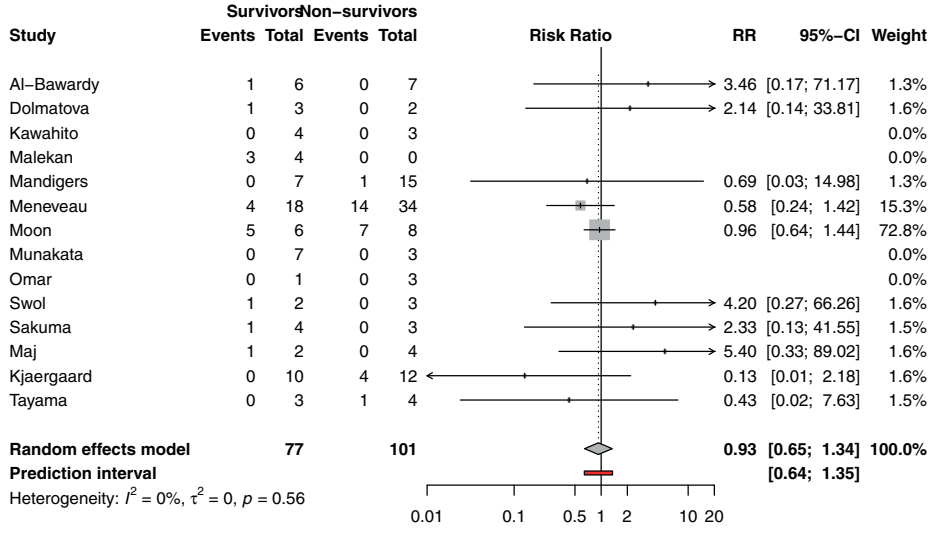
C) Catheter directed therapy



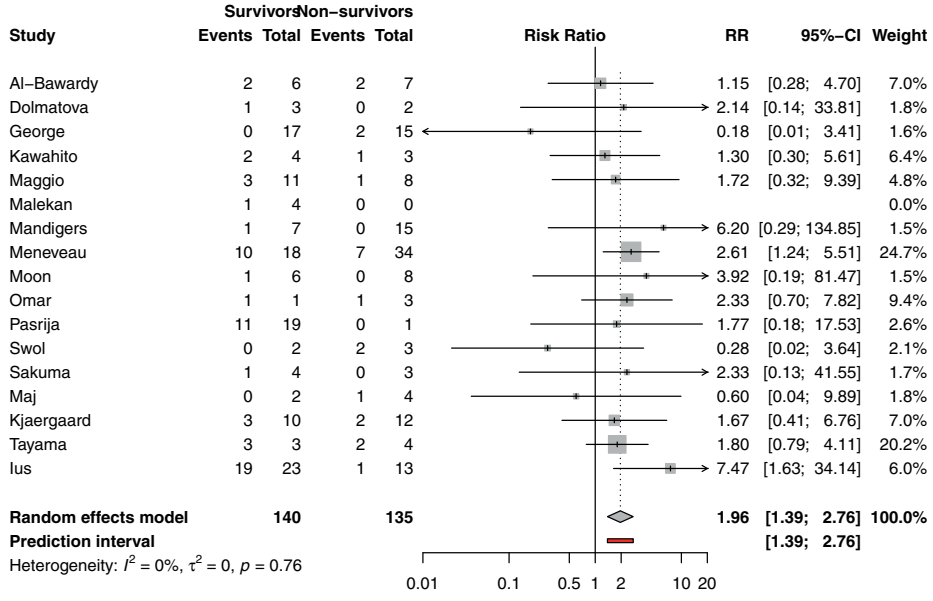
D) Male sex



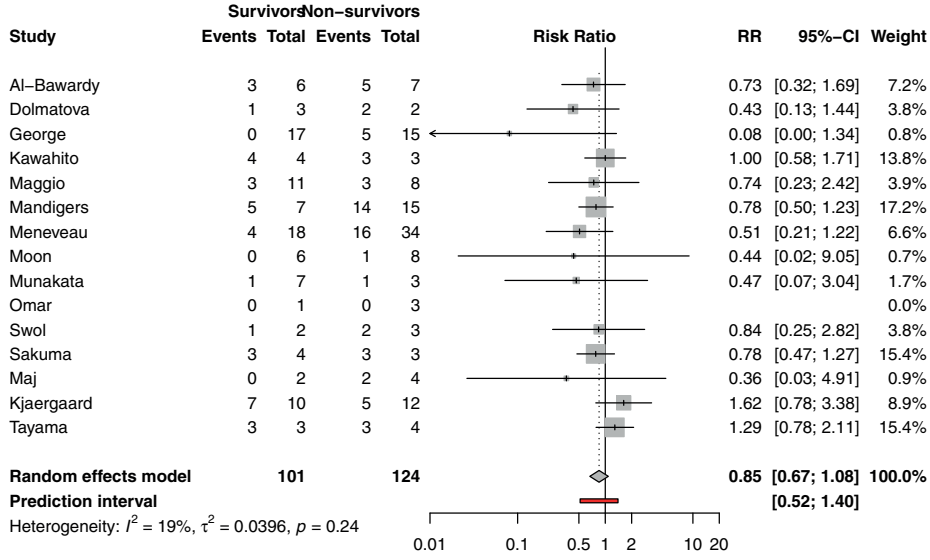
E) Only ECMO treatment



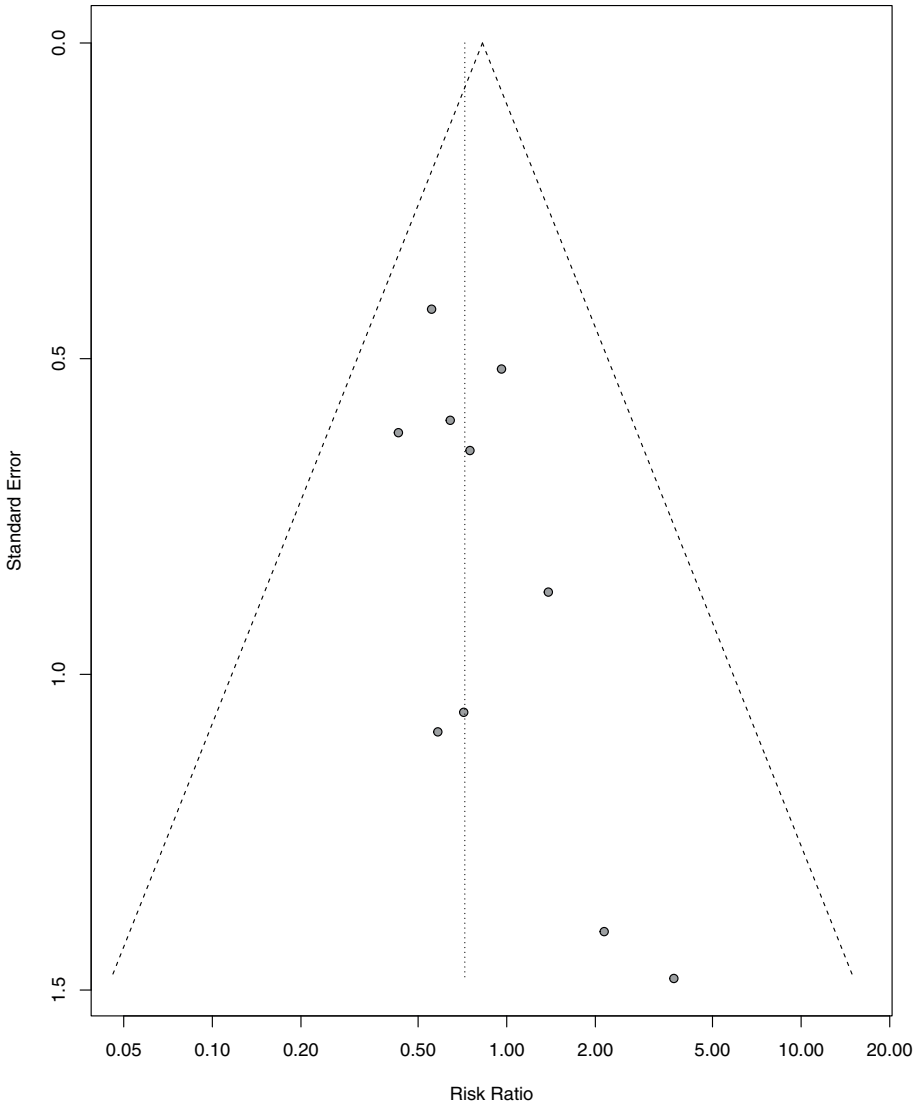
F) Surgical embolectomy



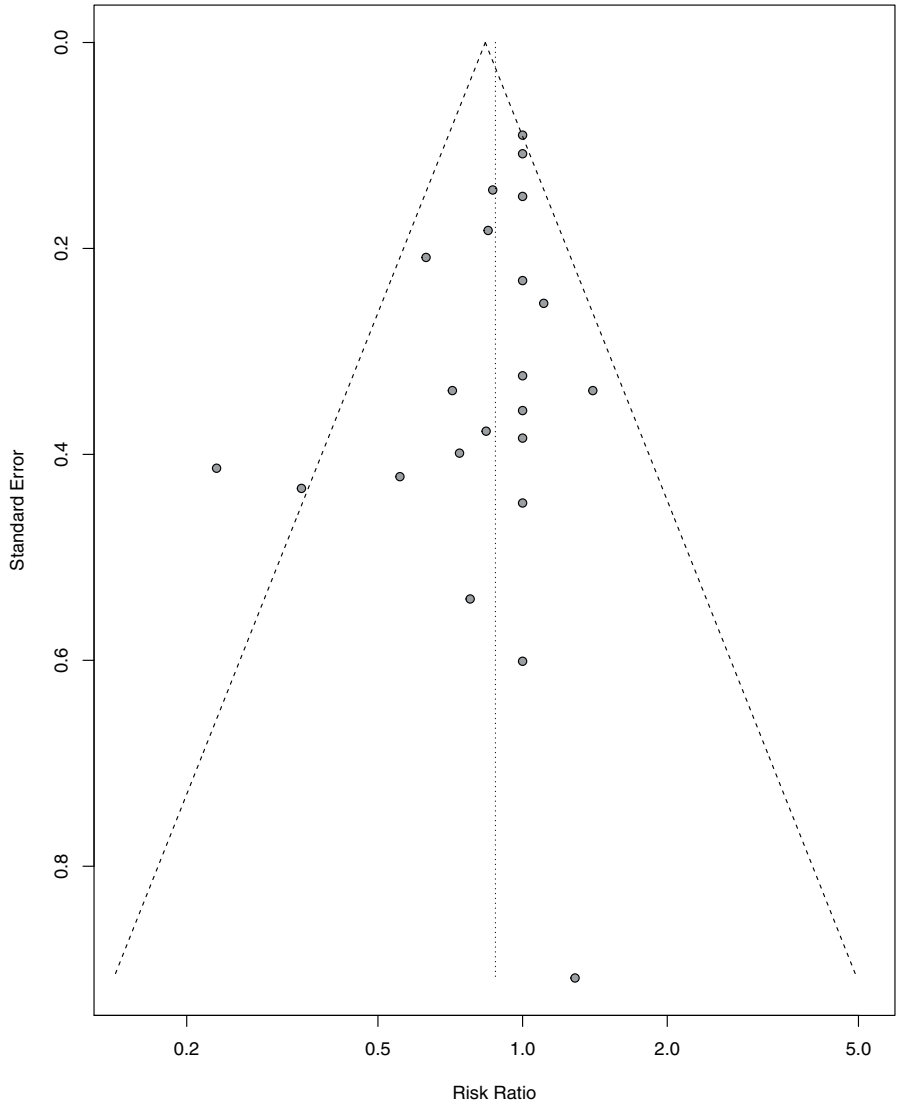
G) Systemic thrombolysis



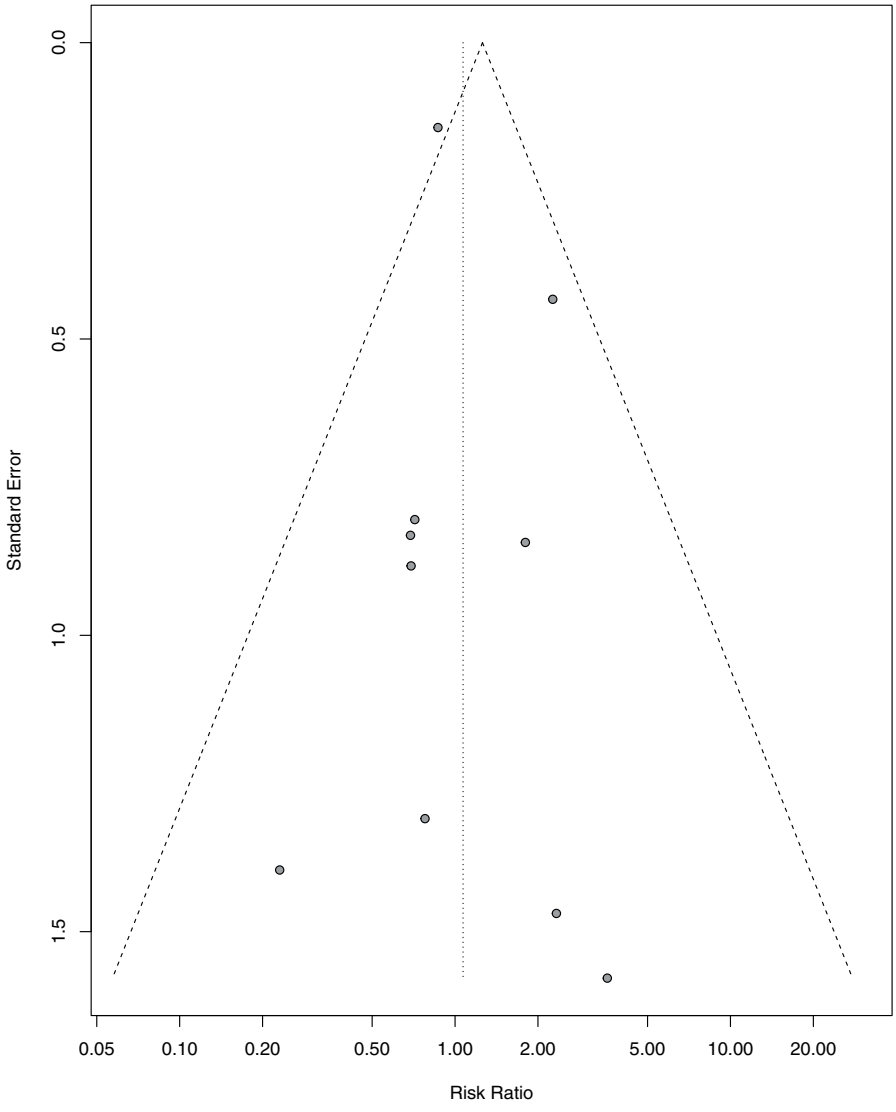
Appendix 4 | Funnel plots of evaluated factors.
A) Age



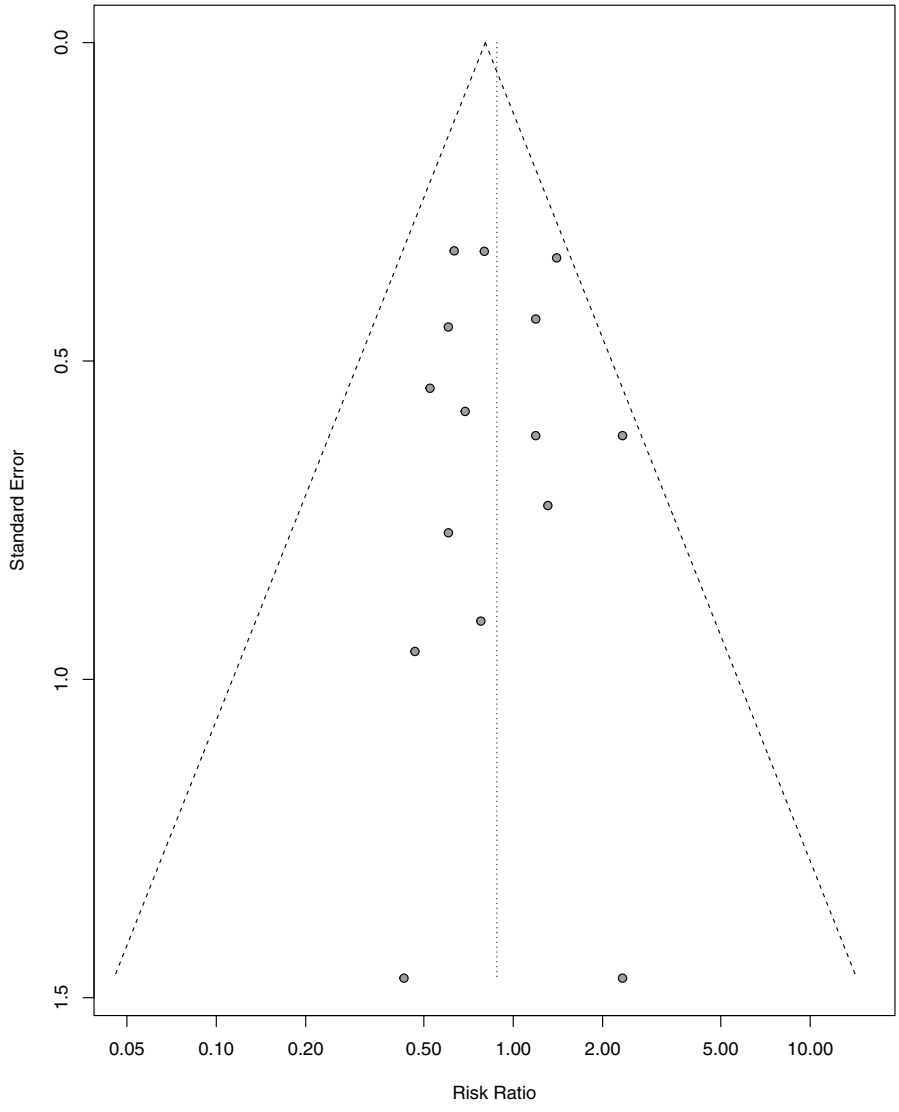
B) Cardiac arrest



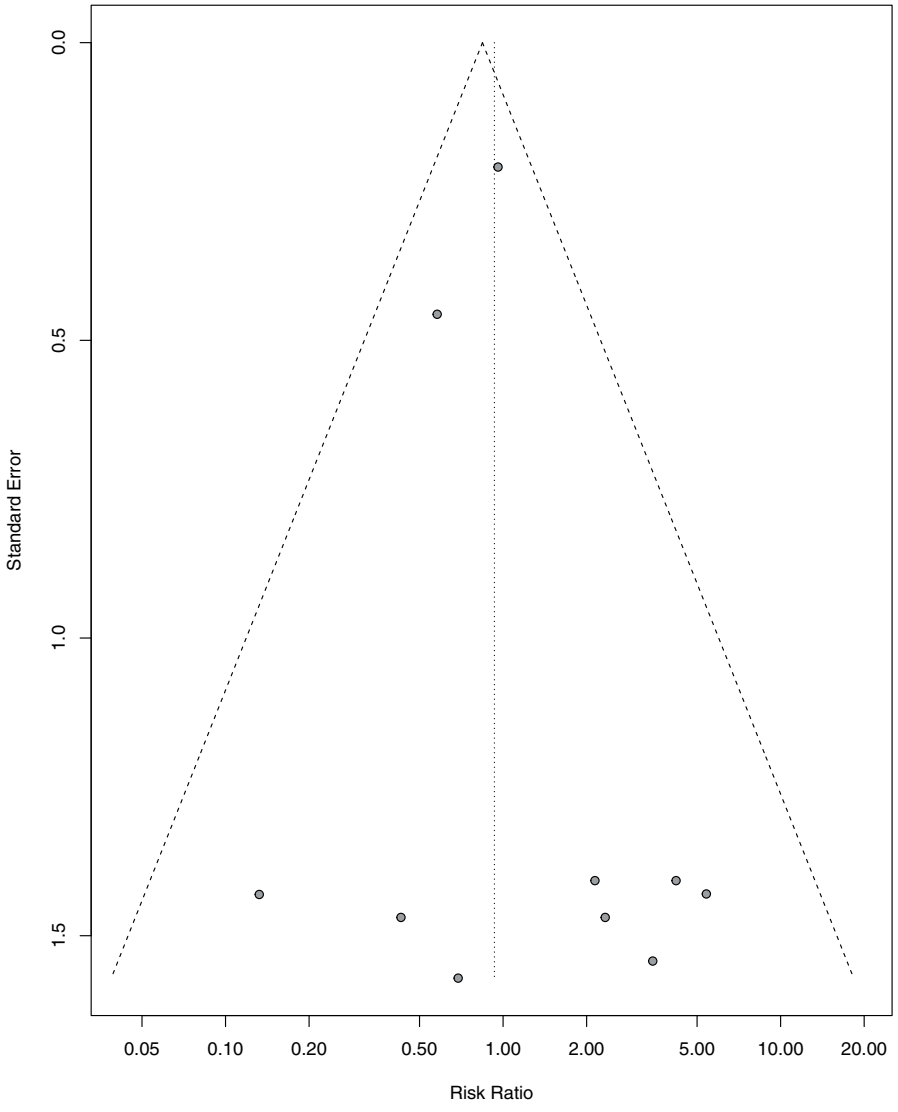
C) Catheter direct therapy



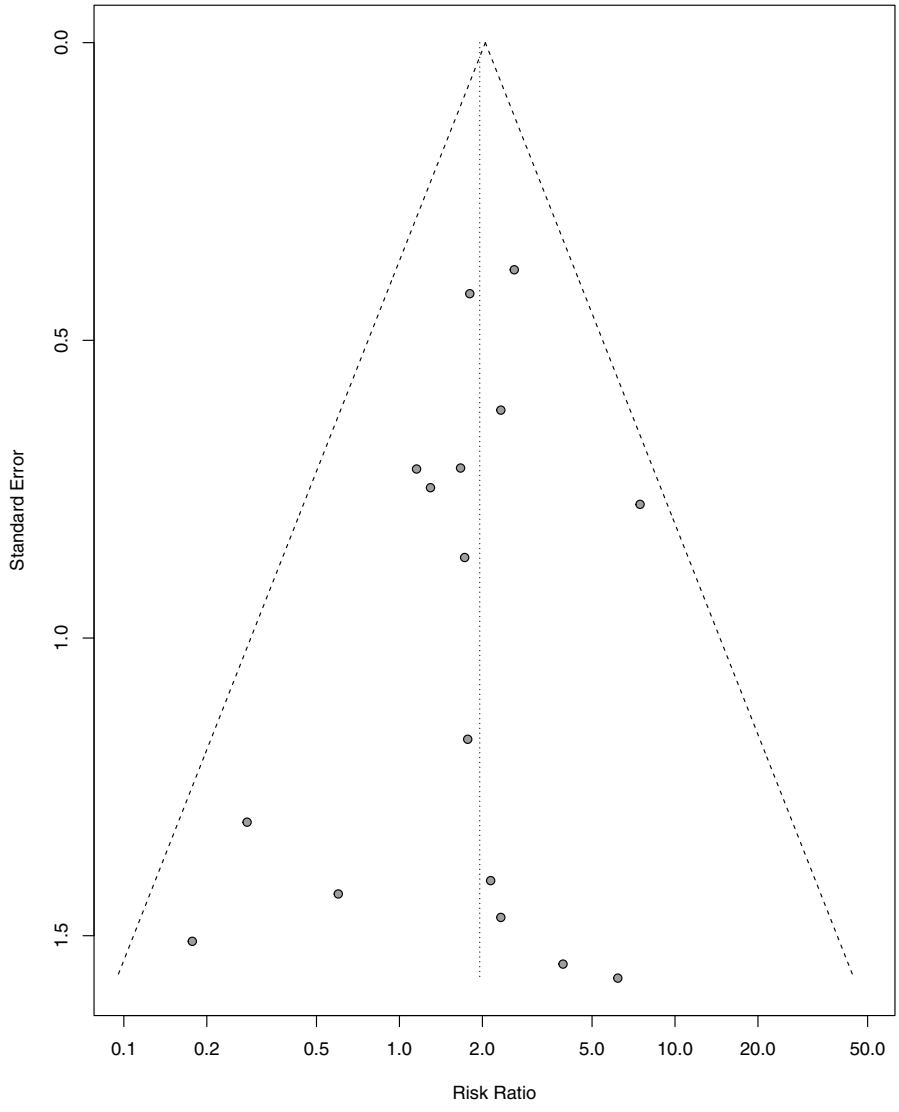
D) Male sex


0.0
0.5
1.0
1.5
Standard Error
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
Risk Ratio

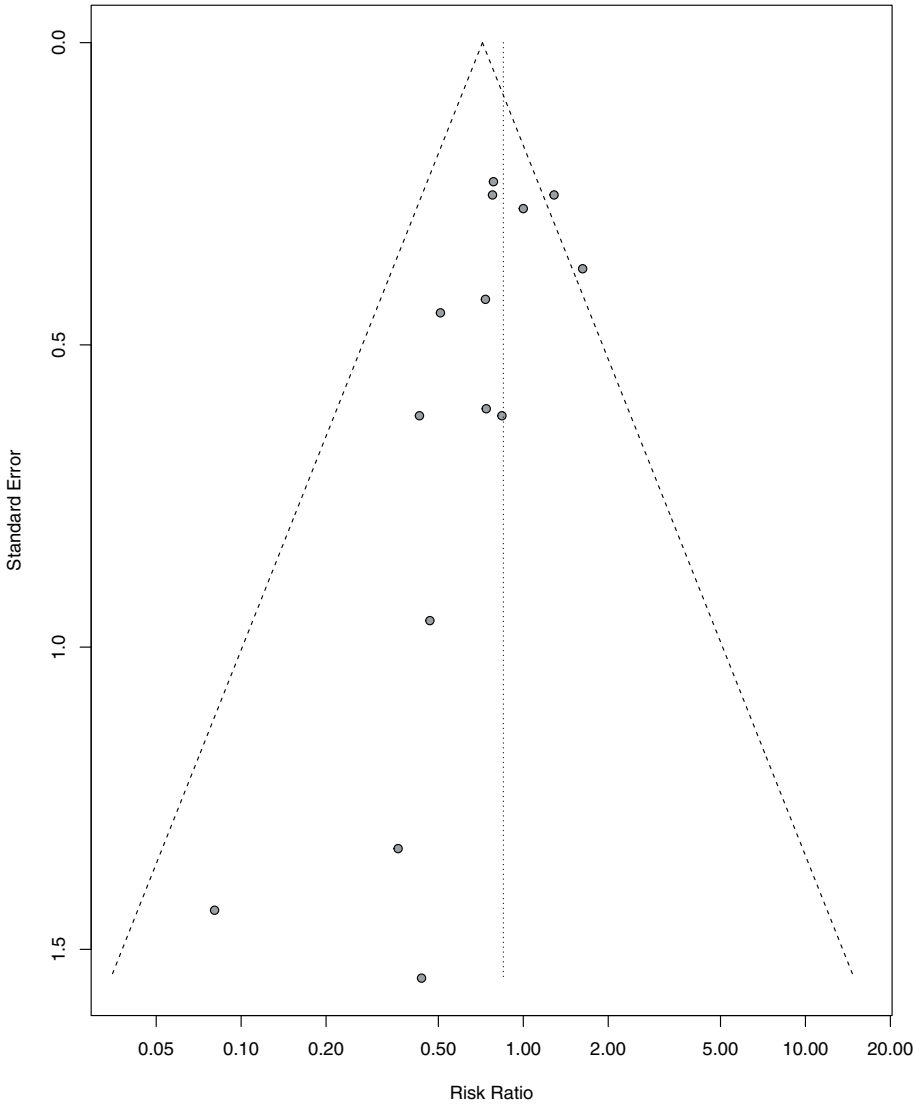
E) Only ECMO treatment



F) Surgical embolectomy

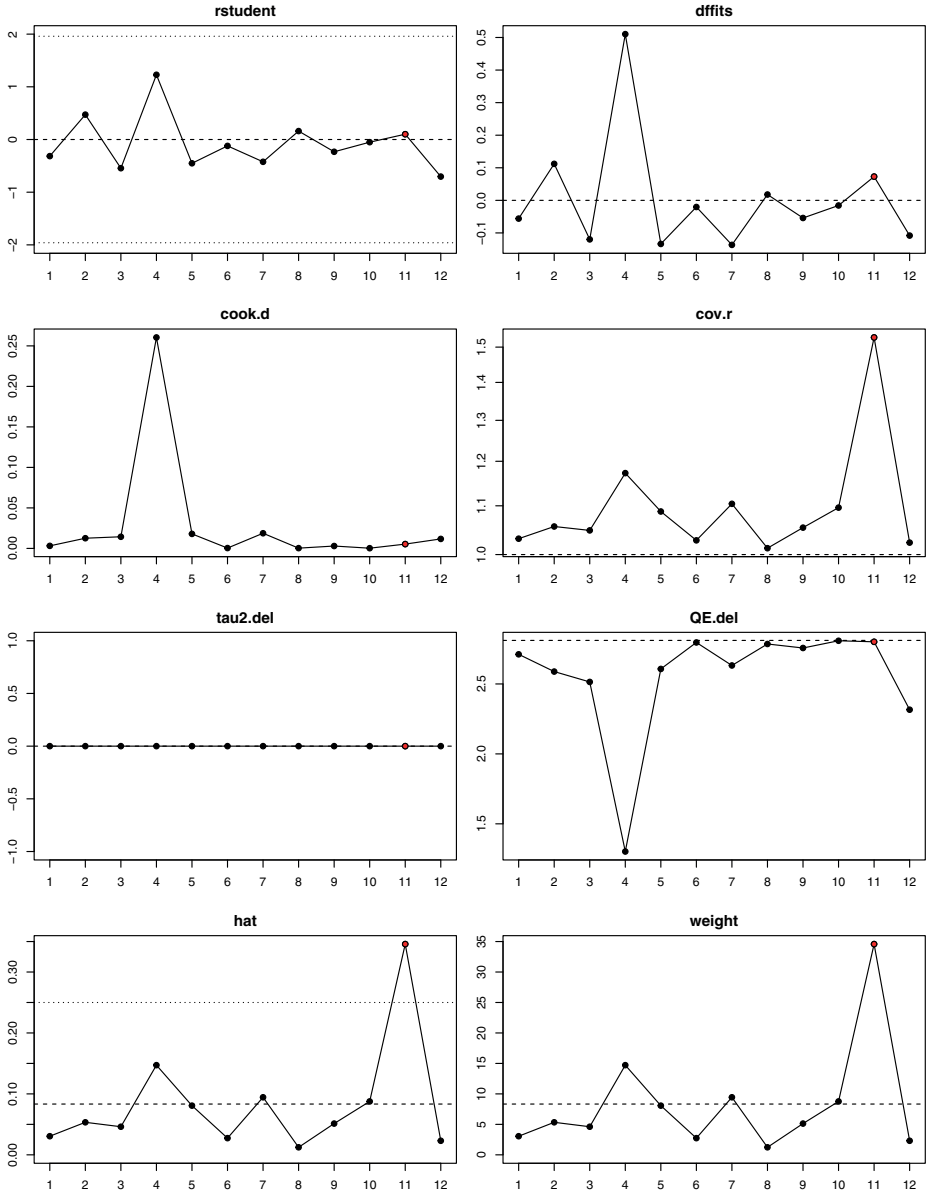


G) Systemic thrombolysis

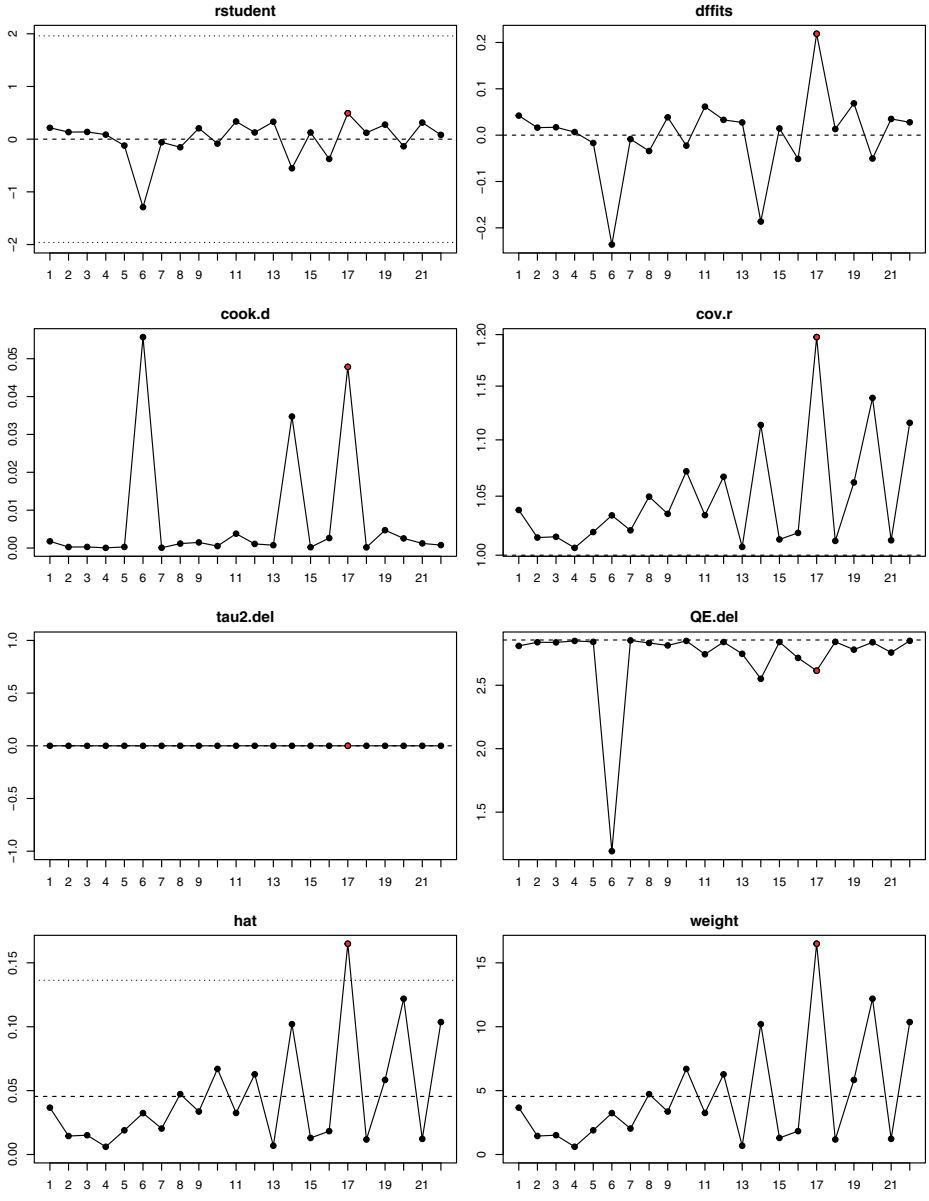


Appendix 5 | Influence plots of evaluated factors.

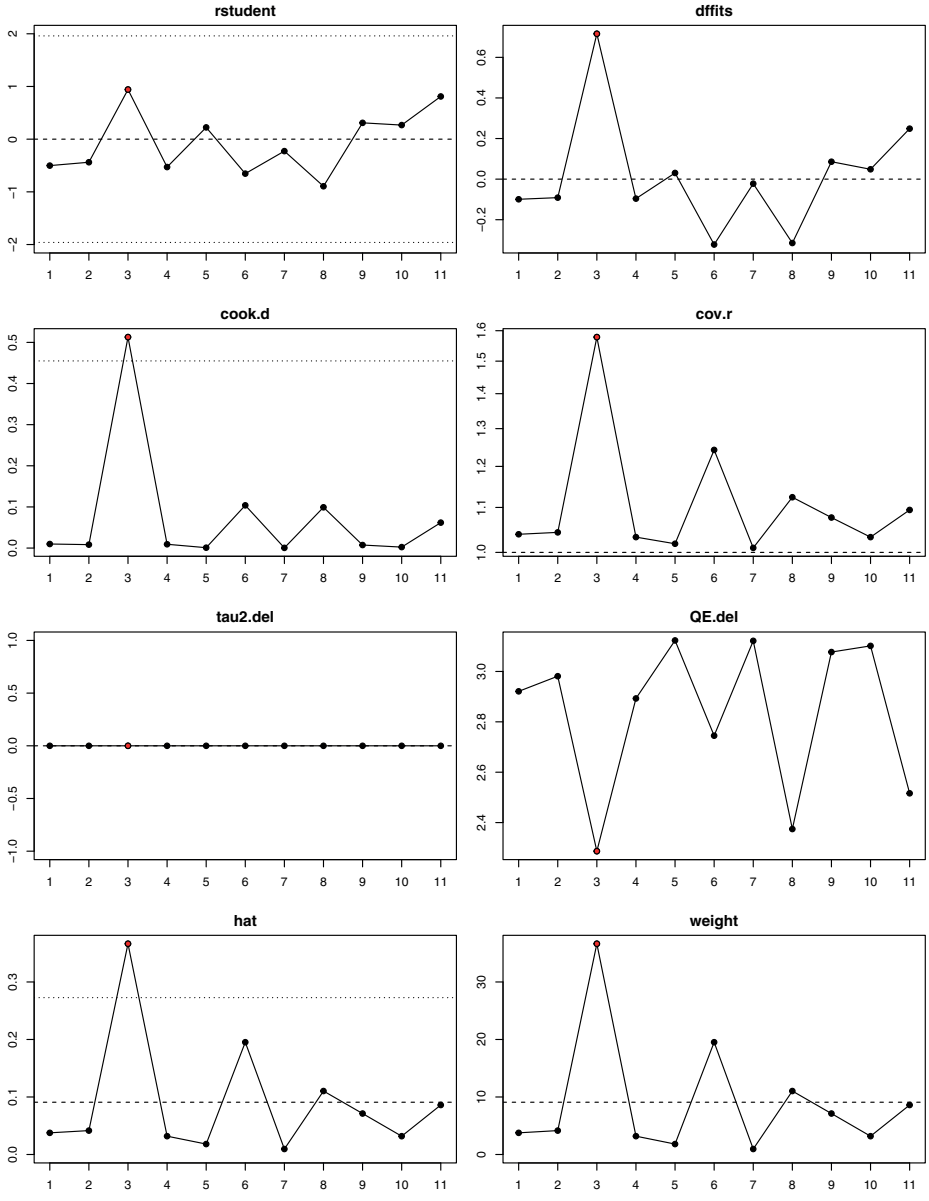
A) Age



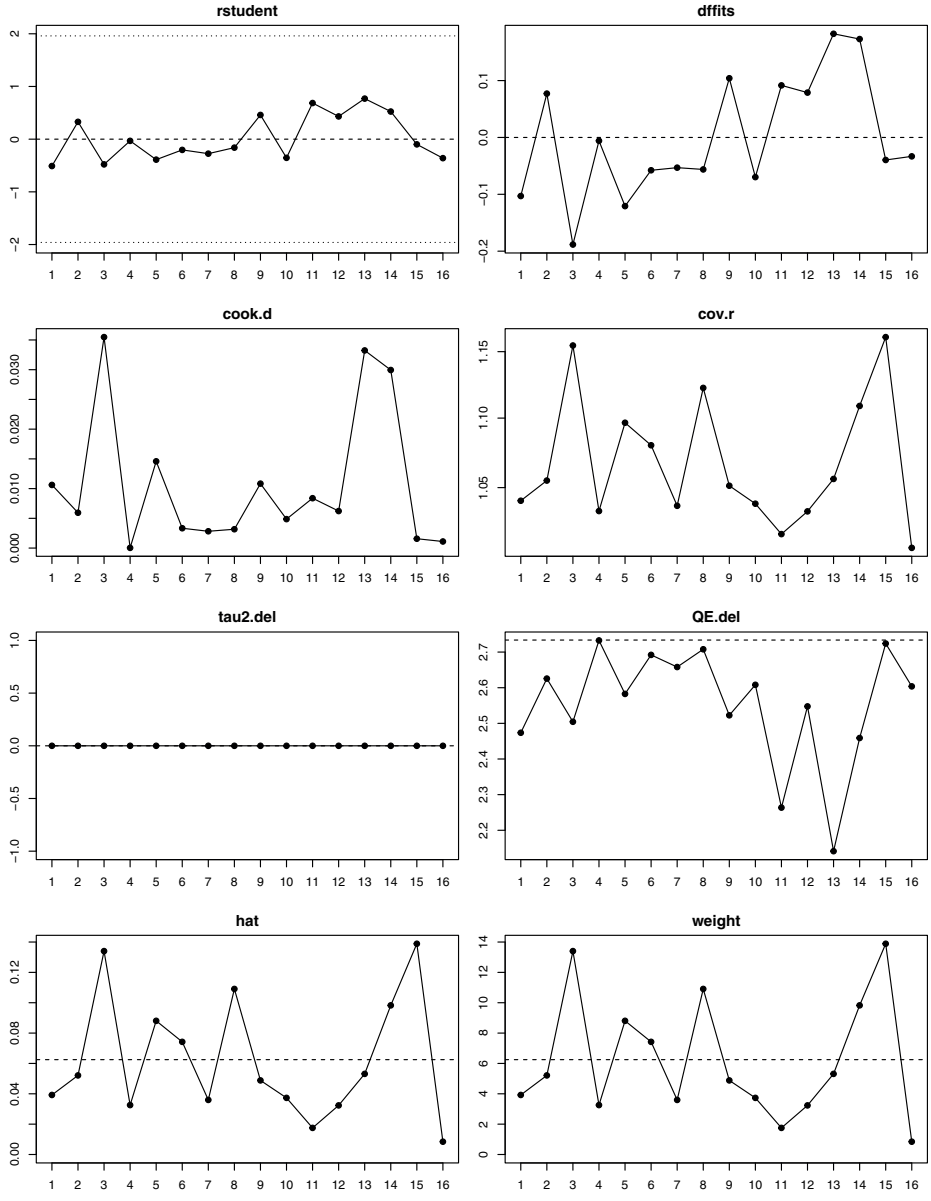
B) Cardiac arrest



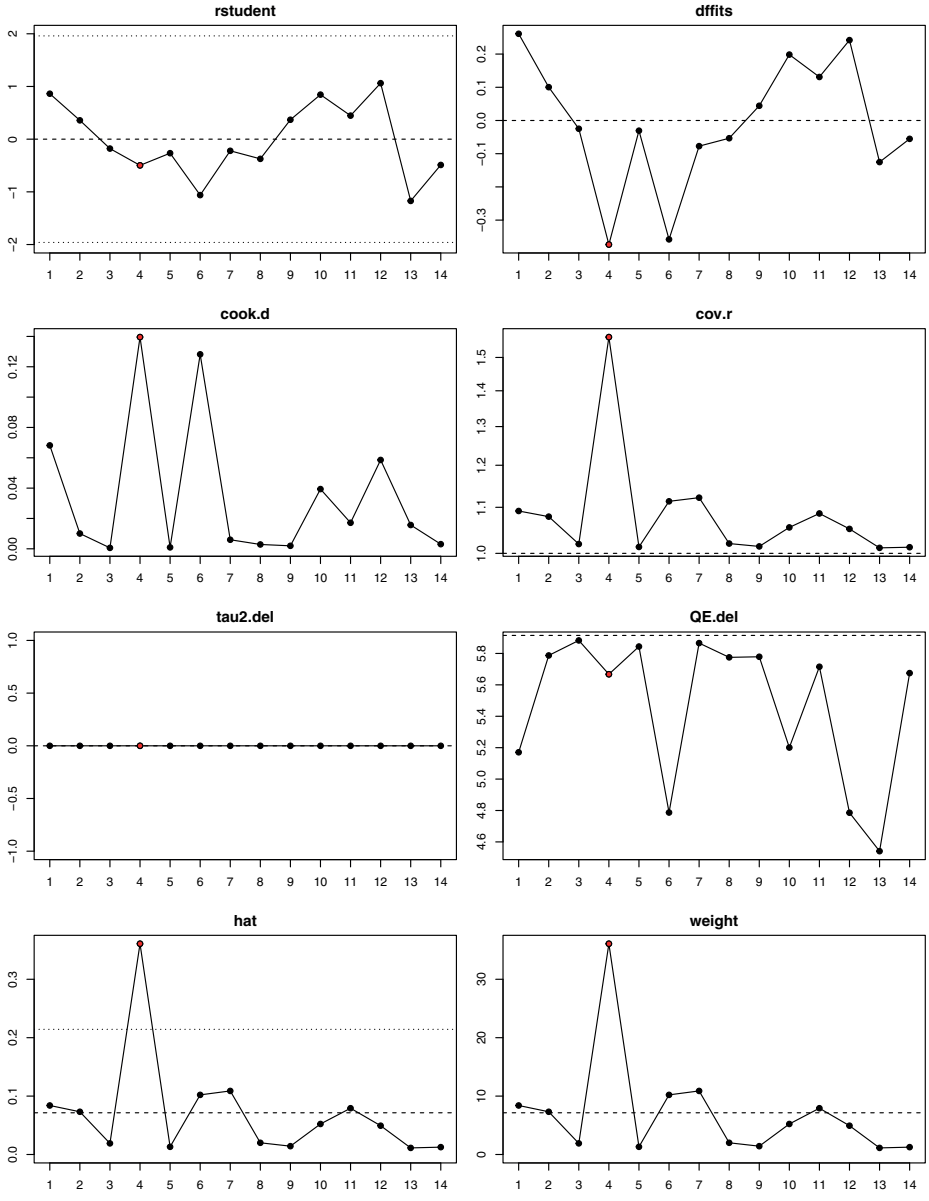
C) Catheter directed therapy



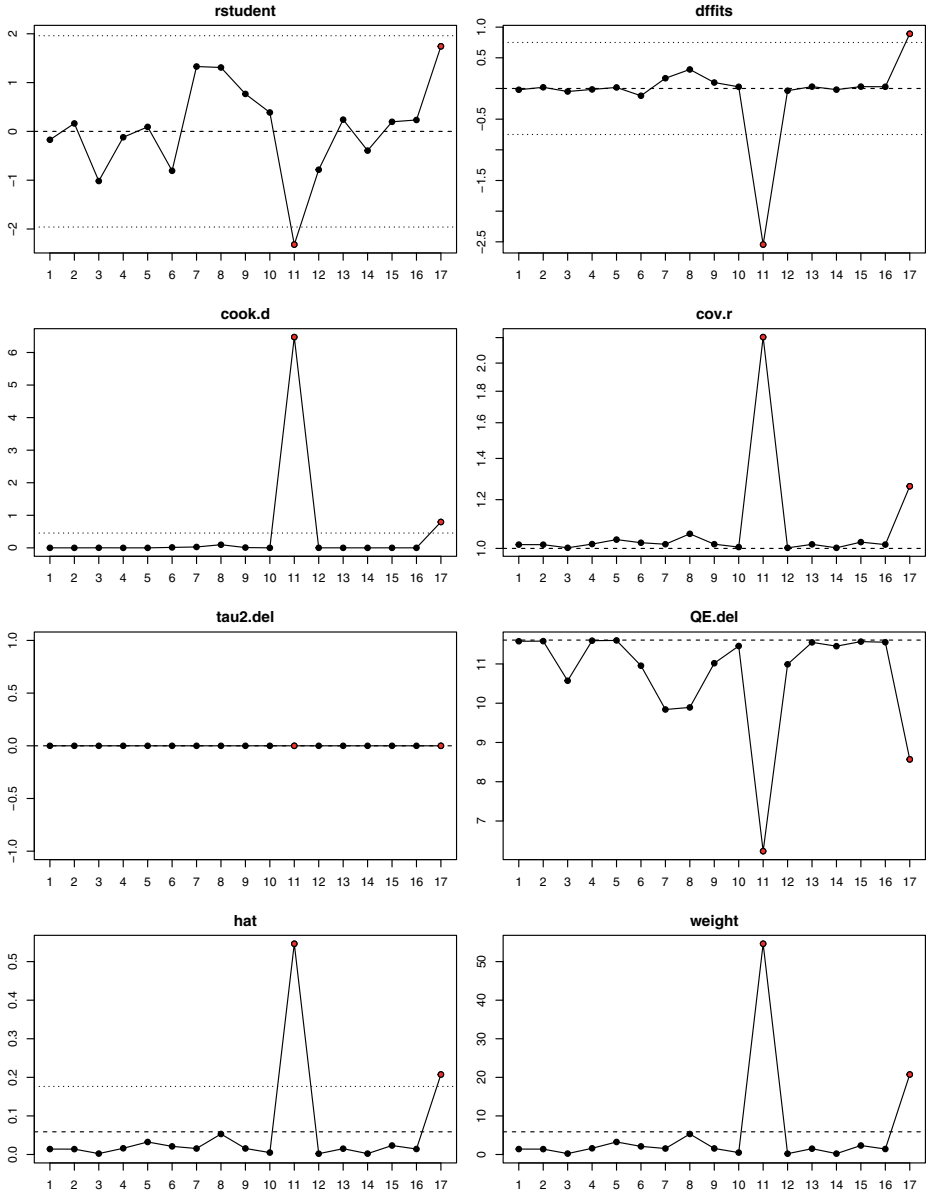
D) Male sex



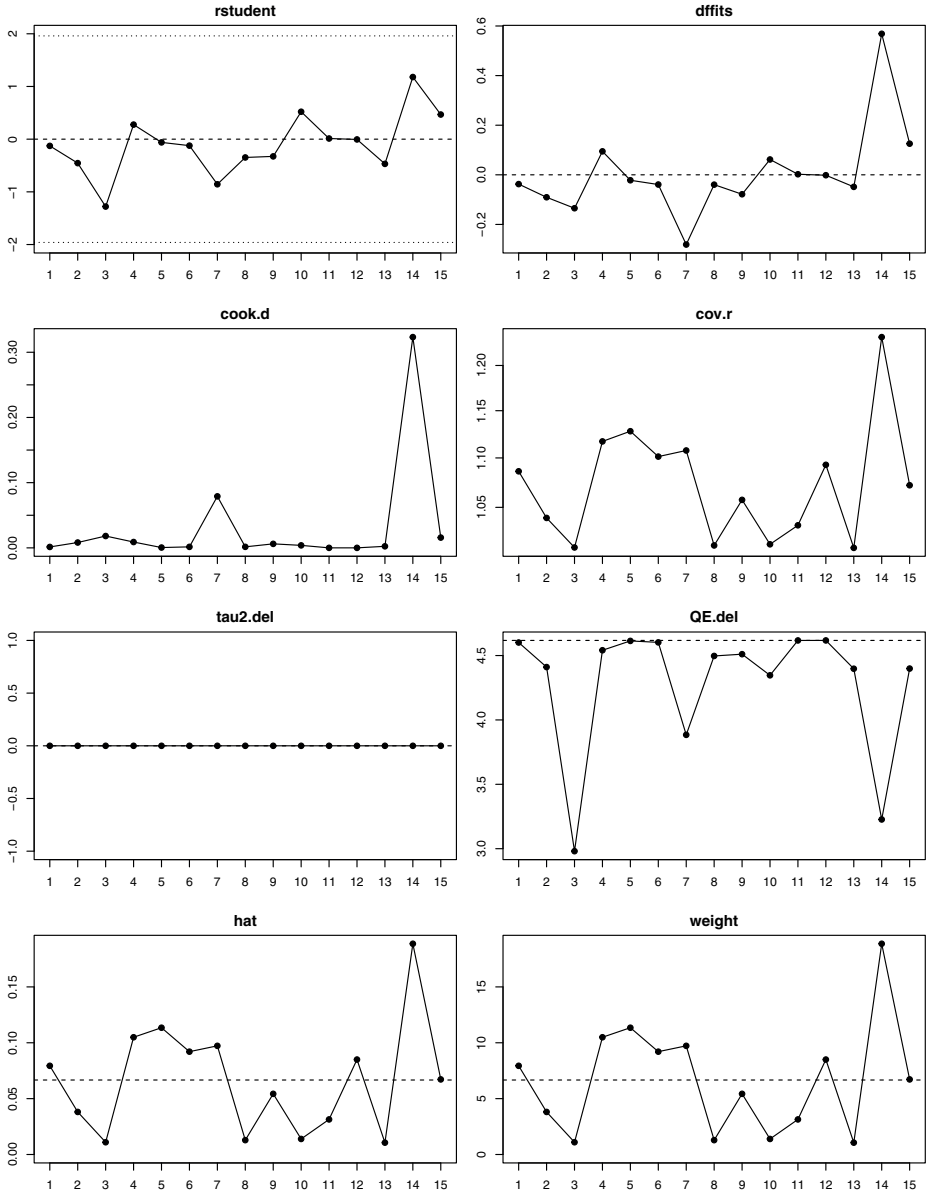
E) Only ECMO treatment



F) Surgical embolectomy



G) Systemic thrombolysis



General Discussion

"Spread your wings, sell your work, don't be afraid to speculate a little, enjoy yourself and make sure you don't just summarise your thesis"- Simon Leather

GENERAL DISCUSSION

Cardiac arrest remains a major cause of death worldwide. Despite the differences in cause of arrest, patient characteristics, and cardiac arrest characteristics (such as primary rhythm, delay until start of cardiopulmonary resuscitation (CPR), low-flow duration (defined as start of CPR until return of spontaneous circulation (ROSC), return of mechanical circulation, or death), and time to first defibrillation), out-of-hospital cardiac arrest (OHCA) as well as in-hospital cardiac arrest (IHCA) have high mortality rates (Table 1).

Table 1 | Mortality rates of OHCA and IHCA patients

	OHCA	IHCA
Overall short term survival	0% - 18% [a]	15% - 34% [b]
Short term survival of patients transported to the hospital	0% - 48% [a]	n.a.
Long term survival		13.4 % [c]
Long term neurological favourable survival		8.3-22.6% [c]

A=(1), B= (2) C = (3)

EPIDEMIOLOGY

In Europe, 84 OHCA per 100,000 adult inhabitants occur annually (range in different areas 28-244 per 100,000). (4) This will probably be an underestimation of the actual number of OHCA, because not every cardiac arrest will be reported (e.g. patients who are already diseased, have a 'do not resuscitate' (DNR) order, or if the emergency medical service (EMS) is not contacted). IHCA occurs in 1.5-1.8 per 1000 adult hospital admissions in Europe annually. (5, 6) This will also be an underestimation of the actual IHCA number, because many in-hospital cases patients already have a DNR order due to age and comorbidity and therefore no resuscitation attempt will be performed. Additionally, in patients in whom the diagnosis causing the admission or complications during admission are severe, treatment will be withdrawn due to futility.

The number of OHCA patients transported to hospitals will most probably increase over the years. The gain of public knowledge regarding cardiac arrest and how to respond to it, will enhance the number of succeeded resuscitations, which will result in a larger number of OHCA patients admitted to the emergency department. The number of IHCA patients could also increase. While the medical knowledge is expanded and more severe illnesses can be treated, these therapies could cause complications leading to IHCA and the patients that are treated could be in worse condition. Therefore, research and developments for both OHCA and IHCA are important.

CARDIAC ARREST PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT

A large part of cardiac arrest research focusses on pre-hospital characteristics in OHCA patients. This mounting research has resulted in an increase in bystander CPR, use of automated external defibrillator (AED), public awareness and education, and shortened time until first defibrillation. (7) However, another important subgroup to be studied should be cardiac arrest patients admitted to the Intensive Care Unit (ICU). This is an important group to study, because of their vulnerability as they need intensive care treatment in contrary to patients admitted to a cardiology ward. Additionally, these patients have return of circulation and, depending on the damage that has already occurred, in-hospital treatment could possibly contribute to the neurological outcome.

Mortality rates of patients admitted to the ICU after cardiac arrest, differs from the overall mortality data. Patients without return of spontaneous circulation (ROSC) or return of circulation (ROC) are not taken into account in these outcomes and therefore these mortality rates are lower than the overall mortality rates. In OHCA, the short-term mortality rates differ between countries/regions worldwide. In French ICUs short-term mortality rate is 66%, in the United Kingdom 61.6%-63.7%, in the United States of America 56% (for OHCA combined with IHCA), in the Netherlands 50.5%, and in New-Zealand and Australia 45.6%. (8-11) (this thesis) These differences in short-term survival rates could be explained by the difference in public awareness, education, AED use, and transport times. However, it is still unknown if these factors are the only contributing factors. There might also be a difference in genetics, treatment strategy, number of patients surviving until admission to the ICU, and maybe many more. International collaboration and comparison of treatment could contribute to better understanding of cardiac arrest pathology and treatment.

Recent large studies aiming on mortality of IHCA patients admitted to the ICU are limited. Regional differences in mortality rates of IHCA patients differ less than those of OHCA patients. Suggesting that pre-hospital differences could contribute more than in-hospital treatment in regard to outcomes. Short-term mortality rates are in the United Kingdom around 60%, in Australia 52.8%, and in the Netherlands 50.3% (12, 13) (this thesis) Recent studies reporting nationwide long-term mortality rates of IHCA patients are even more limited. In the Netherlands, the 1-year mortality rate was 59% in IHCA patients. (this thesis) As for OHCA, also in IHCA research it would be informative to collaborate between international resuscitation/ICU databases in order to study the causes of international differences and eventually improve post-IHCA care.

SEX DIFFERENCES

Sex differences appear to be a very important factor in physiology, pathophysiology, and disease development. In the cardiovascular system genetic, epigenetic, and hormonal effects influence the endothelial and vascular smooth muscle cell, which affects the atherosclerotic process. (14) This could lead to hypertension and atherosclerosis, resulting in higher probabilities of developing coronary artery stenosis. With this, myocardial infarction or cardiac arrest due to ischaemia could occur.

OHCA as well as IHCA occur more often in men than in women. 34-37% of OHCA occur in women, a little lower percentage of those women (25-30%) are admitted to the ICU. (15-18) (this thesis) Crude numbers show higher mortality rates in women. However, mostly this difference disappears or even results in higher mortality rates in men when corrected for baseline and cardiac characteristics. (15-18) (this thesis) Approximately 38% of the IHCA occur in women. Short and long term mortality rates of women suffering an IHCA are higher than in men, for crude numbers as well as adjusted for baseline and cardiac characteristics. (19) (this thesis)

The reason for the sex differences is still not completely known. In women suffering from cardiac arrest, the primary cardiac rhythm is more often non shockable than in men. This is a partly explanation of the difference in crude mortality rates, disappearing when corrected for primary rhythm. This difference in primary rhythm might be due to longer time to start CPR, as shockable rhythm could have changed to non-shockable. Next, it could be that the reason for cardiac arrest in women is more often respiratory failure than in men. (20) Another reason for the difference in outcome for women and men could be hormonal differences. Some studies speculate that female hormones could protect for ischaemia and reperfusion injury. (20) Estrogen could inhibit apoptosis, fibrosis and hypertrophy, promote angiogenesis, act as vasodilatator, and reduces inflammation during ischaemia and reperfusion. (21)

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION VERSUS CONVENTIONAL CARDIOPULMONARY RESUSCITATION

In an attempt to improve outcomes after OHCA and IHCA, placement of an extracorporeal membrane oxygenation (ECMO) during cardiac arrest (i.e. extracorporeal cardiopulmonary resuscitation, ECPR) is studied more and more. This ECPR placement results in early oxygenation and therefore creating time in which the cause of arrest can be analysed and, if possible, treated. Only a small group (10%) of OHCA and IHCA patients will be eligible for ECPR therapy. [Boussaint des amories et al, unpublished] A

standardised protocol and awareness of the treating physicians are crucial for success of this therapy. The most recent ERC guidelines state that there is increasing evidence for the use of ECPR in patients in whom conventional CPR is failing or to facilitate specific interventions. (22)

When comparing ECPR to conventional cardiopulmonary resuscitation (CCPR), restrospective studies show variable results. (22, 23) These difference in results could be caused by difference in experience with ECPR, patient selection, regional difference of genetic characteristics, treatment protocols, and maybe many more. Therefore, some randomised controlled trials (RCTs) were initiated. Unfortunately, the first two RCTs had to be terminated, due to more favourable results in the ECPR group than in the CCPR group. The number of survivors (ECPR 43%, CCPR 7%), and especially survivors who achieved favourable neurological outcomes are significantly higher in the ECPR than in the CCPR treated patients (32-43% versus 0-22%, respectively). (24, 25) This emphasizes the possible advantages of ECPR and the need for studies regarding the best patient selection and ECMO settings resulting in the most favourable neurological outcomes.

ECPR INDICATIONS, PATIENT SELECTION, AND TREATMENT PROTOCOL

Until now, there has been no standardised protocol for ECPR indications, patient selection, and treatment protocol. To achieve the best possible outcomes, this indication, patient selection, and treatment protocol are very important. Most of the ECPR protocols regarding eligible patients are based on local expert opinion rather than evidence based criteria. As stated in the ERC guidelines, there are no universally criteria and inclusion and exclusion criteria of recent trials still differ. (22) Developing studies to provide the best possible criteria for patient selection is hard, due to heterogeneity of patient population, experience with ECPR, small samples, difference in distance to the nearest ECPR centre, and changes of devices/materials which are used. Also, because of the existing local ECPR protocols, the patients who are included in the studies, are already selected based on some patient and cardiac characteristics.

Patient selection

In cardiac arrest research, some patient characteristics which cannot be influenced are known important prognostic factors, such as sex, age, initial cardiac rhythm, and witnessed cardiac arrest. An increasing age will result in decreasing favourable outcomes in both OHCA and IHCA patients. (20, 26, 27). Also in ECPR treated patients, age affects the outcome. (28) However, it is still unknown what the exact upper age level of patients eligible for ECPR should be. Many studies already perform ECPR in a limited age group,

which makes it hard to determine this upper age level. Most upper age limits which are used, are 65-70 years. (22)

For initial cardiac rhythm, it is widely known that patients with initial shockable rhythms have much higher favourable outcomes than patients with initial non-shockable rhythms. (27, 29, 30) However, only including patients with initial shockable rhythms for ECPR would, for example, exclude almost all patients with cardiac arrest due to massive pulmonary embolism (PE), which are very good ECPR candidates, as described in the next paragraph. An unwitnessed cardiac arrest is known for its unfavourable outcome. (27, 29) In both OHCA as well as IHCA, especially with an unknown delay. Therefore, the criterium 'witnessed arrest' could be included in patient selection for ECPR eligibility.

Other important prognostic factors which can or can partially be influenced are for example bystander CPR, time until initiation of CPR, and the duration of resuscitation (i.e. low-flow duration). When bystanders already start to perform CPR, the time until initiation of CPR is as short as possible. Many studies show the importance of bystander CPR on outcomes. (31) In OHCA cases, not witnessed by EMS, initiation of bystander CPR and short no-flow time (≤5 minutes) should be included in patient selection for ECPR initiation.

Treatment protocol

Many ECPR studies focused on selecting patients who will benefit most from ECPR and have favourable neurological outcomes on longer term. However, there is still limited knowledge regarding the treatment protocol of ECPR. When an ECMO is successfully placed during CPR, every hospital or even every physician will determine the ECMO blood flow, gas flow and oxygen suppletion. A standardised protocol, will be hard or even impossible to implicate, because of the individual patient differences. However, several studies did focus on the treatment goals, such as oxygen level and carbon dioxide level.

In our opinion, every patient has to be treated on an individual base, ideally with some set points to aim for. Recently the Extracorporeal Life Support Organization published an interim guideline consensus regarding ECPR patient selection and treatment protocol. (32) These guidelines are partially based on study outcomes and partially on expert opinion. In this guideline, an aimed bloodflow of 3-4L/min is mentioned, however minimum blood flow rates are not known. Second, they mention a mean arterial pressure (MAP) target of ≥ 60mmHg and < 80 mmHg based on animal data. Third, hyperoxia should be avoided, with a recommended target arterial oxygen saturation of 92-97%. Last, hypocarbia should be avoided. (32)

Data in ECPR patients regarding ECMO settings are limited. Therefore, we will first discuss aimed values in CCPR treated patients. In cardiac arrest patients, optimal MAP to preserve brain perfusion post cardiac arrest is still not exactly known. Several stud-

ies report different cut of values, ranging from >65mmHg to >90mmHg. (33) In order to reach this MAP, adrenaline or other vasopressors can be used. A higher MAP using adrenaline, will result in higher cerebral perfusion pressure and higher partial pressure of oxygen in the brain tissue. (34) Remarkably, adrenaline lowers the rSO2 and could result in lower oxygen levels in mitochondria, which is also hypothesized in this thesis. (34) (this thesis) Regarding oxygen suppletion in post cardiac arrest, data is inconclusive. Hypoxemia could have higher mortality rates than hyperoxemia, extremes in oxygen levels could not be associated with neurological outcome, liberal oxygen therapy shows higher mortality rates than conservative. (35-37) Also for carbon dioxide data are inconclusive. Mostly hypocapnia accounts for higher mortality rates than normocapnia and hypercapnia. (11, 29, 36) In some studies, hypercapnia also causes higher mortality rates and in some studies carbon dioxide values or changes do not influence outcomes. (11, 29, 30, 35) (this thesis)

As discussed before, studies regarding ECMO settings related to outcome are limited. For ECPR patients a MAP lower than 65mmHg in the first 6 hours after ECPR initiation, predicts worse neurological outcomes than higher MAP. Start of ECMO flow will already increase the MAP as well as a higher rSO2. (34) The most optimal range of PaO2 should be 77-220mmHg. (38) Hyperoxemia in the first 30 minutes after ECPR initiation will cause higher mortality rates and should be prevented. (39, 40) The course of PaCO2 is not associated with outcome. (41) (this thesis)

EXTRACORPOREAL MEMBRANE OXYGENATION IN PULMONARY EMBOLISM

Massive pulmonary embolisms causes high mortality rates, especially in patients who are in need of cardiopulmonary resuscitation. (42, 43) Many studies already showed that ECMO can be used as effective therapy or bridging method in patients suffering from a massive pulmonary embolism. (44) (this thesis) Using ECMO, the pulmonary embolism can be temporarily bypassed until the embolism is resolved or removed. In order to retrieve the most favourable results, patients with massive pulmonary embolism should be stabilized on VA-ECMO first, before other additional therapies are performed. (45, 46) In a small retrospective study with unequal groups and no multivariate analysis it seemed that the use thrombolysis before ECMO placement will not affect the mortality rate, however it did cause significantly higher number of bleeding complications. (46) A recent systematic review and meta-analysis confirmed that there is no difference in systemic thrombolysis pre-ECMO or no systemic thrombolysis in patients treated with ECMO because of cardiac arrest due to pulmonary embolism. (43) It is still not totally clear if additional therapies have to be combined with ECMO are needed and which

therapy fits best. There are indications that the combination of ECMO and surgical embolectomy provide the best outcomes. (42) (this thesis) However, this data is still limited.

REFERENCES

1. Grasner JT, Wnent J, Herlitz J, Perkins GD, Lefering R, Tjelmeland I, et al. Survival after out-of-hospital cardiac arrest in Europe - Results of the EuReCa TWO study. Resuscitation. 2020;148:218-26.
2. Wnent J, Masterson S, Grasner JT, Bottiger BW, Herlitz J, Koster RW, et al. EuReCa ONE - 27 Nations, ONE Europe, ONE Registry: a prospective observational analysis over one month in 27 resuscitation registries in Europe - the EuReCa ONE study protocol. Scand J Trauma Resusc Emerg Med. 2015;23:7.
3. Schluep M, Gravesteijn BY, Stolker RJ, Endeman H, Hoeks SE. One-year survival after in-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2018;132:90-100.
4. Dutch Guideline Bacterial Meningitis. Dutch Association of Neurology. 2013.
5. Andersen LW, Holmberg MJ, Lofgren B, Kirkegaard H, Granfeldt A. Adult in-hospital cardiac arrest in Denmark. Resuscitation. 2019;140:31-6.
6. Hessulf F, Karlsson T, Lundgren P, Aune S, Stromsoe A, Sodersved Kallestedt ML, et al. Factors of importance to 30-day survival after in-hospital cardiac arrest in Sweden - A population-based register study of more than 18,000 cases. Int J Cardiol. 2018;255:237-42.
7. Blom MT, Beesems SG, Homma PC, Zijlstra JA, Hulleman M, van Hoeijen DA, et al. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. Circulation. 2014;130(21):1868-75.
8. Geri G, Passouant O, Dumas F, Bougouin W, Champigneulle B, Arnaout M, et al. Etiological diagnoses of out-of-hospital cardiac arrest survivors admitted to the intensive care unit: Insights from a French registry. Resuscitation. 2017;117:66-72.
9. Nanayakkara S, Fogarty S, Tremeer M, Ross K, Richards B, Bergmeir C, et al. Characterising risk of in-hospital mortality following cardiac arrest using machine learning: A retrospective international registry study. PLoS Med. 2018;15(11):e1002709.
10. Nolan JP, Orzechowska I, Harrison DA, Soar J, Perkins GD, Shankar-Hari M. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation. 2021;162:304-11.
11. Zhou D, Li Z, Zhang S, Wu L, Li Y, Shi G. Association between mild hypercapnia and hospital mortality in patients admitted to the intensive care unit after cardiac arrest: A retrospective study. Resuscitation. 2020;149:30-8.
12. Jones D, Bhasale A, Bailey M, Pilcher D, Anstey MH. Effect of a National Standard for Deteriorating Patients on Intensive Care Admissions Due to Cardiac Arrest in Australia. Crit Care Med. 2018;46(4):586-93.
13. Nolan JP, Ferrando P, Soar J, Benger J, Thomas M, Harrison DA, et al. Increasing survival after admission to UK critical care units following cardiopulmonary resuscitation. Crit Care. 2016;20(1):219.
14. Seeland U, Nemcsik J, Lonnebakken MT, Kublickiene K, Schluchter H, Park C, et al. Sex and Gender Aspects in Vascular Ageing - Focus on Epidemiology, Pathophysiology, and Outcomes. Heart Lung Circ. 2021;30(11):1637-46.
15. Kotini-Shah P, Del Rios M, Khosla S, Pugach O, Vellano K, McNally B, et al. Sex differences in outcomes for out-of-hospital cardiac arrest in the United States. Resuscitation. 2021;163:6-13.
16. Mody P, Pandey A, Slutsky AS, Segar MW, Kiss A, Dorian P, et al. Gender-Based Differences in Outcomes Among Resuscitated Patients With Out-of-Hospital Cardiac Arrest. Circulation. 2021;143(7):641-9.

17. van Wees C, Rietdijk W, Mandigers L, van der Graaf M, Scholte NTB, Adriaansens KO, et al. Do Women Have a Higher Mortality Risk Than Men following ICU Admission after Out-of-Hospital Cardiac Arrest? A Retrospective Cohort Analysis. J Clin Med. 2021;10(18).
18. Vogelsong MA, May T, Agarwal S, Cronberg T, Dankiewicz J, Dupont A, et al. Influence of sex on survival, neurologic outcomes, and neurodiagnostic testing after out-of-hospital cardiac arrest. Resuscitation. 2021;167:66-75.
19. Stankovic N, Holmberg MJ, Hoybye M, Granfeldt A, Andersen LW. Age and sex differences in outcomes after in-hospital cardiac arrest. Resuscitation. 2021;165:58-65.
20. Al-Dury N, Rawshani A, Karlsson T, Herlitz J, Ravn-Fischer A. The influence of age and gender on delay to treatment and its association with survival after out of hospital cardiac arrest. Am J Emerg Med. 2021;42:198-202.
21. Sun Y, Sangam S, Guo Q, Wang J, Tang H, Black SM, et al. Sex Differences, Estrogen Metabolism and Signaling in the Development of Pulmonary Arterial Hypertension. Front Cardiovasc Med. 2021;8:719058.
22. Soar J, Bottiger BW, Carli P, Couper K, Deakin CD, Djarv T, et al. European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation. 2021;161:115-51.
23. Twohig CJ, Singer B, Grier G, Finney SJ. A systematic literature review and meta-analysis of the effectiveness of extracorporeal-CPR versus conventional-CPR for adult patients in cardiac arrest. J Intensive Care Soc. 2019;20(4):347-57.
24. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. Lancet. 2020;396(10265):1807-16.
25. Napoli N. 'Hyperinvasive' care improves survival in refractory out-of-hospital cardiac arrest, American college of cardiology: American Journal of Cardiology; 2021 [Available from: https://www.acc.org/about-acc/press-releases/2021/05/17/04/23/hyperinvasive-care-improves-survival-in-refractory-out-of-hospital-cardiac-arrest.
26. Al-Dury N, Rawshani A, Israelsson J, Stromsoe A, Aune S, Agerstrom J, et al. Characteristics and outcome among 14,933 adult cases of in-hospital cardiac arrest: A nationwide study with the emphasis on gender and age. Am J Emerg Med. 2017;35(12):1839-44.
27. Fernando SM, Tran A, Cheng W, Rochwerg B, Taljaard M, Vaillancourt C, et al. Pre-arrest and intra-arrest prognostic factors associated with survival after in-hospital cardiac arrest: systematic review and meta-analysis. BMJ. 2019;367:l6373.
28. Marinacci LX, Mihatov N, D'Alessandro DA, Villavicencio MA, Roy N, Raz Y, et al. Extracorporeal cardiopulmonary resuscitation (ECPR) survival: A quaternary center analysis. J Card Surg. 2021;36(7):2300-7.
29. McKenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, et al. Arterial carbon dioxide tension has a non-linear association with survival after out-of-hospital cardiac arrest: A multicentre observational study. Resuscitation. 2021;162:82-90.
30. Peluso L, Belloni I, Calabro L, Dell'Anna AM, Nobile L, Creteur J, et al. Oxygen and carbon dioxide levels in patients after cardiac arrest. Resuscitation. 2020;150:1-7.
31. Al-Dury N, Ravn-Fischer A, Hollenberg J, Israelsson J, Nordberg P, Stromsoe A, et al. Identifying the relative importance of predictors of survival in out of hospital cardiac arrest: a machine learning study. Scand J Trauma Resusc Emerg Med. 2020;28(1):60.

32. Richardson ASC, Tonna JE, Nanjayya V, Nixon P, Abrams DC, Raman L, et al. Extracorporeal Cardiopulmonary Resuscitation in Adults. Interim Guideline Consensus Statement From the Extracorporeal Life Support Organization. ASAIO J. 2021;67(3):221-8.
33. Skrifvars MB, Aneman A, Ameloot K. Individualized blood pressure targets during postcardiac arrest intensive care. Curr Opin Crit Care. 2020;26(3):259-66.
34. Putzer G, Martini J, Spraider P, Abram J, Hornung R, Schmidt C, et al. Adrenaline improves regional cerebral blood flow, cerebral oxygenation and cerebral metabolism during CPR in a porcine cardiac arrest model using low-flow extracorporeal support. Resuscitation. 2021;168:151-9.
35. Ebner F, Riker RR, Haxhija Z, Seder DB, May TL, Ullen S, et al. The association of partial pressures of oxygen and carbon dioxide with neurological outcome after out-of-hospital cardiac arrest: an explorative International Cardiac Arrest Registry 2.0 study. Scand J Trauma Resusc Emerg Med. 2020;28(1):67.
36. McGuigan PJ, Shankar-Hari M, Harrison DA, Laffey JG, McAuley DF. The interaction between arterial oxygenation and carbon dioxide and hospital mortality following out of hospital cardiac arrest: a cohort study. Crit Care. 2020;24(1):336.
37. Young PJ, Bailey M, Bellomo R, Bernard S, Bray J, Jakkula P, et al. Conservative or liberal oxygen therapy in adults after cardiac arrest: An individual-level patient data meta-analysis of randomised controlled trials. Resuscitation. 2020;157:15-22.
38. Chang WT, Wang CH, Lai CH, Yu HY, Chou NK, Wang CH, et al. Optimal Arterial Blood Oxygen Tension in the Early Postresuscitation Phase of Extracorporeal Cardiopulmonary Resuscitation: A 15-Year Retrospective Observational Study. Crit Care Med. 2019;47(11):1549-56.
39. Halter M, Jouffroy R, Saade A, Philippe P, Carli P, Vivien B. Association between hyperoxemia and mortality in patients treated by eCPR after out-of-hospital cardiac arrest. Am J Emerg Med. 2020;38(5):900-5.
40. Munshi L, Kiss A, Cypel M, Keshavjee S, Ferguson ND, Fan E. Oxygen Thresholds and Mortality During Extracorporeal Life Support in Adult Patients. Crit Care Med. 2017;45(12):1997-2005.
41. Lundin A, Dell'anna AM, Peluso L, Nobile L, Annoni F, Creteur J, et al. Veno-arterial CO2 difference and respiratory quotient after cardiac arrest: An observational cohort study. J Crit Care. 2021;62:131-7.
42. L. Hobohm IS, A. Habertheuer, S. Barco, L. Valerio, J. Wild, F.P. Schmidt, T. Gori, T. Münzel, S. Konstantinides, K. Keller,. Clinical Use and Outcome of Extracorporeal Membrane Oxygenation in Patients with Pulmonary Embolism. Resuscitation. 2021.
43. Scott JH, Gordon M, Vender R, Pettigrew S, Desai P, Marchetti N, et al. Venoarterial Extracorporeal Membrane Oxygenation in Massive Pulmonary Embolism-Related Cardiac Arrest: A Systematic Review. Crit Care Med. 2021;49(5):760-9.
44. Chen YY, Chen YC, Wu CC, Yen HT, Huang KR, Sheu JJ, et al. Clinical course and outcome of patients with acute pulmonary embolism rescued by veno-arterial extracorporeal membrane oxygenation: a retrospective review of 21 cases. J Cardiothorac Surg. 2020;15(1):295.
45. Hockstein MA, Creel-Bulos C, Appelstein J, Jabaley CS, Stentz MJ. Institutional Experience With Venoarterial Extracorporeal Membrane Oxygenation for Massive Pulmonary Embolism: A Retrospective Case Series. J Cardiothorac Vasc Anesth. 2021;35(9):2681-5.
46. Prasad NK, Boyajian G, Tran D, Shah A, Jones KM, Madathil RJ, et al. Veno-Arterial Extracorporeal Membrane Oxygenation for Pulmonary Embolism after Systemic Thrombolysis. Semin Thorac Cardiovasc Surg. 2021.

Summary

In this thesis we aimed to study characteristics and outcomes of cardiac arrest patients admitted to the Intensive Care Unit (ICU), the effect of Extracorporeal Cardiopulmonary Resuscitation (ECPR) and especially gas exchange in ECPR treated patients. With this thesis we tried to regain some knowledge if difference in Extracorporeal Membrane Oxygenation (ECMO) settings, and therefore gas exchange, in the first phase after initiation of ECPR could influence neurological outcomes.

In **chapter 2** we found a 1-year mortality rate in out of hospital cardiac arrest (OHCA) patients admitted to the ICU of 56% and 59% in in-hospital cardiac arrest (IHCA) patients. Over the years, this mortality rate statistical significantly declined in OHCA patients, however no statistical significant decline was present in IHCA patients. While focusing more on sex differences in **chapter 3**, women were less likely to be admitted to the ICU after cardiac arrest than men. Of those admitted patients, women had statistical significant higher mortality rates than men for both OHCA 1-year mortality (64% versus 53%, respectively) and hospital mortality (57% versus 47%, respectively), as well as IHCA 1-year mortality (60% versus 57%, respectively) and hospital mortality (52% versus 48%, respectively).

In **chapter 4**, we compared ECPR to conventional cardiopulmonary resuscitation (CCPR) with respect to short-term survival outcomes in relation to low-flow duration. The low-flow duration, i.e. time from cardiac arrest until return of spontaneous circulation, return of extracorporeal circulation, or death, is of major importance in determining outcomes in both ECPR and CCPR treated patients. However, the low-flow duration at which one of both treatment modalities could favour the other remains unclear. In our systematic review and meta-analysis we found a rapid decline of short-term survival in relation to low-flow duration of both ECPR patients and CCPR patients with shockable rhythms in adults as well as children. However, this decline was slower in ECPR patients than in CCPR patients. The low-flow duration at which ECPR favours CCPR is hard to determine, due to lack of individual data and no definition of 'advantage'. In an attempt to determine this difference, we calculated at which low-flow duration the survival outcome was at least 5% higher in ECPR than in CCPR patients with initial shockable rhythms. This difference was present at 16.5 minutes low-flow duration in adults and 19.2 minutes in children.

While zooming in on the gas-exchange during the first period after ECPR initiation, in **chapter 5** we studied continuous mitochondrial partial oxygen pressure (mitoPO$_2$) measurements in pigs treated with ECPR in experimental settings. We showed that continuous measurements of mitoPO$_2$ in a pigs skin is possible in experimental settings. While circulation is stopped, mitoPO$_2$ will decrease rapidly. After ECPR initiation there is a delay in the initial spike of mitoPO$_2$ measurements after this ECPR initiation. This could be a result of centralization (the skin as end organ will be the last part to regain flow) or it could be due to vasopressor use. Next, we found a discrepancy of mitoPO$_2$ and mean

arterial pressure (MAP), which could point to the possible value of additional measurements besides MAP to monitor the tissue perfusion in ECPR patients.

We hypothesized that a rapid oxygen increase and carbon dioxide (CO_2) decrease could cause unfavourable neurological outcomes. In **chapter 6** we focused on cerebral oxygen saturation (rSO_2) of humans treated with ECPR. In this small sample prospective observational study we found a higher mean cerebral rSO_2 in the first 30 minutes after ECPR initiation in patients who regained consciousness than in patients without regain of consciousness. The baseline cerebral rSO_2 measurements, before initiation of ECPR, did not differ between those two groups. Despite our hypothesis, the slope of rSO_2 in the first 30 minutes after ECPR initiation did not influence neurological outcome. Regarding CO_2 levels in ECPR patients, studied in **chapter 7**, we also found no association of the course of partial CO_2 pressure (pCO_2) in the first hours after ECPR initiation and recovery of consciousness. In addition, as well as in rSO_2 values, this study also showed no difference in baseline pCO_2 values. However, both studies had a limited number of survivors, which makes it hard to perform multivariable analyses.

A special circumstance in which ECPR could be used is cardiac arrest due to pulmonary embolism. In **chapter 8** we describe a retrospective study comparing patients with highly suspected or proven massive pulmonary embolism treated with ECPR or CCPR. In this study we found a neurological favourable survival in 21% of patients treated with ECPR and 0% in patients treated with CCPR. In a broader perspective, in **chapter 9** we performed a meta-analysis in patients with massive pulmonary embolism, with and without cardiac arrest, treated with ECMO. This study showed insufficient evidence that ECMO treatment improves outcomes in patients with massive pulmonary embolism. However, short-term outcomes are more favourable in patients aged ≤ 60 years and patients who received a surgical embolectomy.

CLINICAL IMPLICATIONS

In our perspective, taking the above mentioned data into account, low-flow duration should be as short as possible, aiming for a low-flow duration of maximum 60 minutes until ECPR is initiated. In practise this should result in starting ECPR placement after a maximum of 45-50 minutes low-flow duration. In patients treated with ECPR, the focus of hemodynamic monitoring should not only be MAP but also other ways of monitoring tissue perfusion. Whenever it is possible, patients treated with ECPR should receive the least as possible amount of vasopressors in order to prevent ischaemia due to reduced perfusion.

After initiating ECPR, the main goal should be to normalise the oxygen and carbon dioxide levels as soon as possible. In order to manage this, arterial blood gases should

be taken frequently and the ECMO should be adapted accordingly. In patients with cardiac arrest due to pulmonary embolism, ECPR should be considered at all times. With ECMO initiation, anticoagulation will be used and therefore one could consider to skip thrombolysis in these patients, to prevent major bleedings caused by ECMO placement and during ECMO therapy. If patients with massive pulmonary embolisms treated with ECMO are still hemodynamically unstable, a surgical embolectomy could contribute to more favourable outcomes.

FUTURE PERSPECTIVE

Whenever the data of all randomised controlled trials comparing ECPR and CCPR is available, individual low-flow duration data should be studied to determine the best time frame at which ECPR favours CCPR. In order to limit low-flow durations in cardiac arrest patients, the implication of an ECMO 'in the field' should be tested in the Netherlands. The most convenient way to organise this, would be placing ECMO-devices on Lifeliners (i.e. helicopters used for medical emergencies, with a specialised physician and specialised nurse present) in the Netherlands. This way a limited group, i.e. the specialised physicians, need to be trained and will get enough exposure to get experience in ECPR procedures. It will most probably also be important to limit the 'time in the field', which makes routine ECPR training even more crucial in order to make this work.

To improve ECPR therapy, tissue perfusion measurements should be included in these patients. Therefore, studies aiming to find the best additional measurement in these patients should be initiated. This way information about the best ECMO settings for ECPR patients could be retrieved. One of the additional measurements should be continuous rSO_2 measurements. When these measurements are performed on a larger scale, comparing different ECMO treatment strategies, it could attribute to the current knowledge. To study this different treatment strategies, randomised controlled trials could be initiated to retrieve more, and hopefully individualised, information of ECMO settings resulting in the most favourable outcomes.

As randomised controlled trials comparing ECPR and CCPR are now focussed on cardiac causes, it would be informative to perform randomised controlled trials comparing ECPR and CCPR in patients with cardiac arrest due to pulmonary embolisms. In patients with massive pulmonary embolism, additional therapies which can be used together with ECMO treatment should be studied, to find the best possible treatment combination for these patients.

Samenvatting

Het doel van deze thesis was om onderzoek te doen naar: (1) de karakteristieken en uitkomsten van patiënten opgenomen op de Intensive Care (IC) na een hartstilstand, (2) het effect van Extracorporale Cardiopulmonale Resuscitatie (ECPR) bij deze patiënten en (3) in het bijzonder de effecten van de gaswisseling door middel van het gebruik van ECPR. We hebben met deze thesis geprobeerd kennis te verkrijgen over het mogelijke effect van verschillende Extracorporale Membraan Oxygenatie (ECMO) standen, en daarmee wederom de gaswisseling, in de eerste fase na initiatie van ECPR op de neurologische uitkomst.

In **hoofdstuk 2** hebben we een 1-jaars mortaliteit gevonden van 56% bij patiënten die buiten het ziekenhuis gereanimeerd worden (out-of-hospital cardiac arrest, OHCA) en daarna opgenomen worden op de IC. Deze 1-jaars mortaliteit was 59% bij patiënten die in het ziekenhuis gereanimeerd werden (in-hospital cardiac arrest, IHCA). Gedurende de jaren is deze mortaliteit statistisch significant gedaald bij de OHCA patiënten, maar bij IHCA patiënten werd geen statistisch significante daling gezien. Wanneer we ons in **hoofdstuk 3** richten op verschillen in geslacht, zien we dat er minder vrouwen dan mannen opgenomen worden op de IC na een hartstilstand. Van deze patiënten was er bij OHCA patiënten een statistisch significant hogere mortaliteit bij vrouwen dan bij mannen in zowel de 1-jaars mortaliteit (64% versus 53%, respectievelijk) en ziekenhuis mortaliteit (57% versus 47%, respectievelijk). Ook bij IHCA patiënten was dit verschil te zien voor 1-jaars mortaliteit (60% versus 57%, respectievelijk) en ziekenhuis mortaliteit (52% versus 48%, respectievelijk).

In **hoofdstuk 4** hebben we ECPR vergeleken met conventionele cardiopulmonale resuscitatie (CCPR) op basis van korte termijn overleving in relatie tot lage-flow duur. Deze lage flow duur, i.e. tijd vanaf hartstilstand tot terugkeer van spontane circulatie, terugkeer van extracorporale circulatie of tot overlijden, is een belangrijke determinant voor de uitkomst van zowel ECPR als CCPR patiënten. Het is nog onduidelijk vanaf welk exact moment van lage flow duur één van deze behandelopties beter is dan de ander. Met onze systematische review en meta-analyse vonden we een snelle daling van korte-termijn overleving in relatie tot lage flow duur voor zowel ECPR als CCPR met een schokbaar primair cardiaal ritme bij volwassenen en bij kinderen. Deze daling in korte-termijn overleving was echter langzamer bij ECPR dan bij CCPR patiënten. Het bepalen van de lage flow duur waarbij ECPR betere resultaten heeft dan CCPR is lastig. Dit komt door het gebrek aan individuele data en het missen van een definitie van 'betere resultaten'. In onze systematische review hebben we een poging gedaan om dit verschil vast te leggen en hebben we gekeken wanneer de korte-termijn overleving van ECPR minimaal 5% hoger was dan van CCPR met primair schokbaar ritme. Dit verschil was aanwezig vanaf 16.5 minuten lage flow duur bij volwassenen en 19.2 minuten lage-flow duur bij kinderen.

Als we wat meer inzoomen op de gaswisseling in de eerste periode na het starten van ECPR, bestuderen we in **hoofdstuk 5** de continue mitochondriale partiele zuurstof spanning ($mitoPO_2$) metingen in varkens die ECPR ondergingen. Hierbij zagen we dat deze continue metingen van $mitoPO_2$ in de huid van varkens in een experimentele setting mogelijk is. Als de circulatie stopt, daalt de $mitoPO_2$ in de huid zeer snel. Na het starten van ECPR is er een vertraging in de initiële $mitoPO_2$ piek. Deze vertraging zou het resultaat kunnen zijn van centralisatie (de huid zal als eindorgaan het laatste zijn waar de flow terugkeert) of het zou het resultaat kunnen zijn van het gebruik van vasopressoren. De vasopressoren zouden kunnen zorgen voor een verminderde perfusie van het perifere vaatbed. Daarnaast vonden we een discrepantie van $mitoPO_2$ en gemiddelde arteriële druk (mean arterial pressure, MAP), wat het belang benadrukt van eventiele additionele metingen naast de MAP ter monitoring van weefselperfusie bij ECPR patiënten.

Onze hypothese was dat snelle stijging van zuurstof en een snelle daling van koolstofdioxide (CO_2) zouden kunnen resulteren in ongunstige neurologische uitkomsten. In **hoofdstuk 6** hebben we gekeken naar het verloop van de cerebrale zuurstof saturatie (rSO_2) bij patiënten die met ECPR behandeld werden. In deze prospectieve observationele studie, in een kleine patiëntengroep, vonden we bij patiënten met herstel van bewustzijn in de eerste 30 minuten na het starten van ECPR een hoger gemiddelde cerebrale rSO_2 dan bij patiënten zonder herstel van bewustzijn. De rSO_2 metingen voor het starten van ECPR (baseline waardes) verschilden niet binnen deze twee groepen. In tegenstelling tot onze eerdergenoemde hypothese, vonden we geen effect van de snelheid van rSO_2 stijging in de eerste 30 minuten na het starten van ECPR op neurologische uitkomst. Het verloop van CO_2 waardes bij patiënten behandeld met ECPR hebben we bestudeerd in **hoofdstuk 7**. Hierbij vonden we geen associatie van het verloop van de partiele CO_2 spanning (pCO_2) in de eerste uren na het starten van ECPR met het herstel van bewustzijn. Ook was er geen sprake van een verschil van baseline pCO_2 waardes voor het starten van ECPR. Echter, bij beide studies (rSO_2 en pCO_2) was er sprake van een klein aantal overlevende patiënten, waardoor multivariabele analyses onvoldoende uitgevoerd konden worden.

Een specifieke aandoening waarbij ECPR ingezet kan worden is wanneer er sprake is van een hartstilstand veroorzaakt door een massale longembolie. In **hoofdstuk 8** presenteren we een retrospectieve studie waarbij we een vergelijking maken tussen ECPR en CCPR bij patiënten met een hoge verdenking op of een bewezen massale longembolie. Bij deze studie vonden we een goede neurologische overleving van 21% van de patiënten behandeld met ECPR en 0% bij patiënten behandeld met CCPR. In een breder perspectief hebben we in **hoofdstuk 9** een meta-analyse gedaan met studies die patiënten includeerden met een massale longembolie, met of zonder hartstilstand, die behandeld zijn met ECMO. Deze studie laat zien dat er onvoldoende bewijs is om vast te

stellen dat ECMO de uitkomsten van patiënten met een massale longembolie verbeterd. Wel was het zo dat korte termijn uitkomsten beter waren in patiënten van 60 jaar of jonger en patiënten die tevens een chirurgische embolectomie ondergingen.

KLINISCHE IMPLEMENTATIE

Met de bovengenoemde resultaten in overweging nemend, is het in ons perspectief vooral belangrijk om de lage-flow duur zo kort mogelijk te houden en als doel te hebben om de ECPR tot het moment van draaien van de flow niet langer te laten duren dan 60 minuten. In de praktijk zal dit betekenen dat het starten van het plaatsen van ECPR na maximaal 45-50 minuten lage-flow duur zal moeten gebeuren. Bij de patiënten die behandeld worden middels ECPR zou de hemodynamische monitoring zich niet alleen moeten focussen op de MAP maar zullen er meer parameters die iets zeggen over de weefselperfusie gemonitord moeten worden. Wanneer mogelijk, moet er zo min mogelijk gebruik gemaakt worden van vasopressoren in patiënten die behandeld worden middels ECPR, vanwege het mogelijke effect ervan op de perfusie.

Na de initiatie van ECPR is het belangrijkste doel om de zuurstof en koolstofdioxide waarden zo snel mogelijk naar normaalwaardes te krijgen. Om dit te bewerkstelligen (en ook niet door te schieten naar te hoge/lage waardes) zullen er frequent arteriële bloedgasanalyses plaats moeten vinden zodat de ECMO aangepast kan worden naar aanleiding van deze waardes. Wanneer patiënten een hartstilstand hebben die veroorzaakt wordt door een massale longembolie, zou ECPR ten alle tijden overwogen moeten worden. Wanneer een ECMO geplaatst is, zal er altijd antistolling gegeven worden. Vandaar dat er, bij patiënten met een reanimatie door een massale longembolie waarbij besloten is te behandelen middels ECPR, overwogen moeten worden om geen thrombolyse te geven. Er is daardoor een kleinere kans op bloedingscomplicaties. Bij een patiënt met een massale longembolie die behandeld wordt met ECMO waarbij er persisterend sprake is van hemodynamische instabiliteit, kan een chirurgische embolectomie bijdragen aan een betere uitkomst.

TOEKOMSTPERSPECTIEVEN

Wanneer alle data van de gerandomiseerde gecontroleerde studies waarbij ECPR en CCPR vergeleken worden beschikbaar is, zouden individuele lage flow data bestudeerd moeten worden. Daarmee kan er een betere uitspraak gedaan worden over het beste tijdswindow waarbij ECPR betere uitkomsten geeft dan CCPR. Om de lage-flow duur van een reanimatie te beperken, zou er (meer) onderzoek gedaan moeten worden naar

het plaatsen van een ECMO op locatie, met name in Nederland. De beste manier om dit in Nederland te onderzoeken zou zijn om ECMO-apparaten aan boord van de Traumahelikopter te plaatsen en alle traumahelikopter artsen de procedure eigen te laten maken. Op deze manier leert een kleine groep artsen (gespecialiseerd traumahelikopter artsen) de procedure en zullen daarmee ook voldoende ervaring met ECPR op doen en onderhouden. Hierbij moet er wel in acht genomen worden dat de pre-hospitale tijd ook gelimiteerd moet worden. Routine ECPR training zal cruciaal zijn om dit te laten slagen.

Om de ECPR therapie te verbeteren, zou het goed zijn om weefselperfusiemetingen uit te voeren bij deze patiënten. Studies naar de beste additionele meetmethodes bij ECPR patiënten zouden van toegevoegde waarde zijn. Hiermee zou meer informatie gevonden kunnen worden over de ECMO instellingen met de beste uitkomsten voor ECPR patiënten. Een voorbeeld van een meting die kan bijdragen, is de continue rSO_2 meting. Als deze metingen op grotere schaal uitgevoerd worden (met grotere patiëntgroepen) en er verschillende ECMO behandelingsstrategieën vergeleken worden, zou dit bijdragen aan de huidige kennis. De verschillende behandelingsstrategieën zouden via gerandomiseerde gecontroleerde studies vergeleken moeten worden. Hiermee zal meer en wellicht ook meer individuele informatie beschikbaar komen over ECMO instellingen die leiden tot de beste uitkomsten.

Er zijn nu enkele gerandomiseerde studies (bijna) afgerond die ECPR en CCPR vergelijken. Deze zijn vooral gericht op cardiale oorzaken van een hartstilstand. Een interessante aanvulling hierop zou een gerandomiseerde gecontroleerde studie zijn die ECPR en CCPR vergelijkt bij patiënten die een hartstilstand hebben, veroorzaakt door een massale longembolie. Bij patiënten met een massale longembolie, met en zonder een hartstilstand, zouden aanvullende behandelingen, die tegelijk met ECMO behandeling gegeven kunnen worden, onderzocht moeten worden. Dit om de beste behandelcombinatie voor deze patiënten te vinden.

About the author

Loes Mandigers was born on the 21th of May 1988 in Valkenswaard, Noord-Brabant. After finishing secondary school at Were-Di she studied Medicine at University of Maastricht from 2007-2013. She started working at the Surgery department of the Erasmus Medical Center as resident not in training (ANIOS) for one year. Because of her interest in acute care she worked for 9 months as ANIOS at the intensive Care Unit of Sint Elisabeth Hospital in Tilburg. Afterwards she worked for 1.5 years as ANIOS at the IJsselland hospital at several departments (Intensive Care Unit, Cardiology, Emergency Department, Pulmonology, Internal Medicine, Gastro-enterology). While working at the Intensive Care Unit of the IJsselland hospital she met dr. dos Reis Miranda and got the opportunity to start this PhD at the ErasmusMC, under supervision of Prof.dr. Gommers, dr. dos Reis Miranda, and dr. den Uil. At the end of this PhD-project, she worked as ANIOS at the Intensive Care Unit of the ErasmusMC for a few months because of the first COVID episode. After finishing around 3.5 years of full time PhD work, she worked as ANIOS at the Cardiology department of Maasstad hospital and she is currently working as ANIOS at the Cardiology department of the ErasmusMC. Loes lives together with Michiel in Berkel en Rodenrijs.

PhD portfolio

ERASMUS UNIVERSITY ROTTERDAM

PHD PORTFOLIO

Loes Mandigers

Description	Organizer	EC
Required		
COEUR: Intensive Care Part I (2017)		0.50
Erasmus MC - CPO-course: Patient Oriented Research (2017)	Erasmus MC Graduate School	0.30
COEUR PhD-day 2017 (2017)		0.40
EURO-ELSO Maastricht (2017)		0.90
Erasmus MC - BROK® (Basic course Rules and Organisation for Clinical researchers) (2017)		1.50
Erasmus MC - EndNote workshop (2017)		0.20
COEUR Keynote-lectures (2017)	COEUR	0.20
Erasmus MC - Scientific Integrity (2017)	Erasmus MC Graduate School	0.30
COEUR: Intensive Care Part II (2017)		0.50
GIK dag (fellows IC) (2017)		0.30
Research Integrity (2017)	ErasmusMC	0.30
PhD-day 2017 (2017)		0.30
Open Clinica course (2017)		0.30
EMC - ESP03 Introduction to Data-analysis (2017)		1.40
METC Meeting (2017)		0.10
Thesis workshop (2018)	ErasmusMC	0.10
Wetenschapsmiddag AAV (2018)		0.20
COEUR PhD-day 2018 (2018)		0.30
EURO-ELSO Prague (2018)	EURO-ELSO	0.90
Erasmus MC - Basic Introduction Course on SPSS (2018)		1.00
PhD-day 2018 (2018)		0.30
EMC - CC02 Biostatistical Methods I: Basic Principles (2018)		5.70
EMC - EP03 Biostatistical Methods II: Classical Regression Models (2018)		4.30
Presentation Characteristics Cardiac Arrest patients (2018)	Stichting NICE	0.80
Introduction Hora Finita (2019)	COEUR	0.10
Cardiovascular ACE day (2019)		0.30
ISICEM congress Brussels (2019)		1.40
EURO-ELSO Barcelona (2019)	EURO-ELSO	1.40
COMET meeting (2019)	Bert Mik	0.30
VENA workshop “Keep cool and focused” (2019)	VENA	0.20
Refereeravond “Drugs in acute care” (2019)	SEH	0.10

PhD-day 2019 (2019)		0.30
ELSO Baltimore (2019)	ELSO	1.20
Erasmus MC - Biomedical English Writing and Communication (2020)		3.00
Refereeravond “De sporter op de spoed” (2020)	SEH	0.10
Research meetings / PhD meetings (2020)		2.40
Optional		
Presentation MOFE/ECPR (2017)		0.10
Presentation COOSI/Anaconda (2017)		0.10
ATLS Refresher course (2017)		0.50
Training Nurses for MOFE study (2018)		0.30
Presentation ECPR in pulmonary embolism patients (2018)		0.10
Invited seminar COMET measurements (Universitätsklinikum Freiburg) (2019)		0.50
Cursus Persoonlijk Leiderschap (2020)	ErasmusMC	1.20
Supervising two Master students (2020)		1.00
		------ +
Total EC		**35.70**

List of publications

Mandigers L, Scholten E, Rietdijk WJR, den Uil CA, van Thiel RJ, Rigter S, Heijnen BGADH, Gommers D, Dos Reis Miranda D. Survival and neurological outcome with extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest caused by massive pulmonary embolism: A two center observational study. Resuscitation. 2019 Mar;136:8-13. doi: 10.1016/j.resuscitation.2018.12.008. Epub 2018 Dec 17. PMID: 30572065.

Mandigers L, Epker JL. A case report of iatrogenic deterioration of yet undiagnosed Rhombencephalitis; always be careful with corticoids. BMC Clin Pathol. 2018 Dec 27;18:15. doi: 10.1186/s12907-018-0083-2. PMID: 30602941; PMCID: PMC6307248.

den Uil CA, Ligthart JMR, **Mandigers L**, den Dekker WK. Cocaine/amphetamine-induced accelerated atherosclerosis, coronary spasm and thrombosis, and refractory ventricular fibrillation. Eur Heart J Case Rep. 2019 Dec;3(4):1-2. doi: 10.1093/ehjcr/ytz167. Epub 2019 Sep 24. PMID: 31911992; PMCID: PMC6939810.

Mandigers L, den Uil CA, dos Reis Miranda D. Extracorporale cardiopulmonale resuscitatie (ECPR). A&I, nummer 4, dec 2019

Mandigers L, Termorshuizen F, de Keizer NF, Gommers D, Dos Reis Miranda D, Rietdijk WJR, den Uil CA. A nationwide overview of 1-year mortality in cardiac arrest patients admitted to intensive care units in the Netherlands between 2010 and 2016. Resuscitation. 2020 Feb 1;147:88-94. doi: 10.1016/j.resuscitation.2019.12.029. Epub 2020 Jan 8. PMID: 31926259.

Rietdijk WJR, **Mandigers L**, den Uil CA. Mortality Risk Factors for Cardiac Arrest Prior to Venoarterial Extracorporeal Membrane Oxygenation. Crit Care Med. 2020 Feb;48(2):e155. doi: 10.1097/CCM.0000000000004028. PMID: 31939818.

Rietdijk W, **Mandigers L**, Bakker J. Do perceived honorary authors influence publication chance? Survey evidence from the journal of critical care. J Crit Care. 2020 Dec;60:202-208. doi: 10.1016/j.jcrc.2020.05.010. Epub 2020 May 30. PMID: 32871417.

Rietdijk WJR, **Mandigers L**, den Uil CA. A Reconciliation Attempt of the Acute Coronary Syndrome Clinical Trials on Clopidogrel, Prasugrel, and Ticagrelor. Cardiovasc Drugs Ther. 2020 Jun;34(3):439-441. doi: 10.1007/s10557-020-06955-5. PMID: 32215776.

Mandigers L, den Uil CA, Bunge JJH, Gommers D, Dos Reis Miranda D. Initial Arterial pCO2 and Its Course in the First Hours of Extracorporeal Cardiopulmonary Resuscitation Show No Association with Recovery of Consciousness in Humans: A Single-Centre

Retrospective Study. Membranes (Basel). 2021 Mar 15;11(3):208. doi: 10.3390/membranes11030208. PMID: 33804283; PMCID: PMC8001427.

Mandigers L, D. Reis Miranda. Exploring a new world with mechanical circulatory support during cardiac arrest: the horizon of extracorporeal cardiopulmonary resuscitation. Neth J Crit Care - Volume 28, No 4, Jul 2020

den Uil CA, **Mandigers L**, Rietdijk WJR. Letter by den Uil et al Regarding Article, "Improved Survival With Extracorporeal Cardiopulmonary Resuscitation Despite Progressive Metabolic Derangement Associated With Prolonged Resuscitation". Circulation. 2020 Aug 25;142(8):e119-e120. doi: 10.1161/CIRCULATIONAHA.120.046300. Epub 2020 Aug 24. PMID: 32833520.

Karami M*, **Mandigers L***, Miranda DDR, Rietdijk WJR, Binnekade JM, Knijn DCM, Lagrand WK, den Uil CA, Henriques JPS, Vlaar APJ; DUTCH ECLS Study Group. Survival of patients with acute pulmonary embolism treated with venoarterial extracorporeal membrane oxygenation: A systematic review and meta-analysis. J Crit Care. 2021 Aug;64:245-254. doi: 10.1016/j.jcrc.2021.03.006. Epub 2021 Mar 24. PMID: 34049258. *contributed equally

van Wees C, Rietdijk W, **Mandigers L**, van der Graaf M, Scholte NTB, Adriaansens KO, van den Berg RCM, den Uil CA. Do Women Have a Higher Mortality Risk Than Men following ICU Admission after Out-of-Hospital Cardiac Arrest? A Retrospective Cohort Analysis. J Clin Med. 2021 Sep 21;10(18):4286. doi: 10.3390/jcm10184286. PMID: 34575397; PMCID: PMC8470772.

Mandigers L, Pooth JS, Wefers Bettink MA, den Uil CA, Damjanovic D, Mik EG, Brixius S, Gommers D, Trummer G, Dos Reis Miranda D. Monitoring Mitochondrial Partial Oxygen Pressure During Cardiac Arrest and Extracorporeal Cardiopulmonary Resuscitation. An Experimental Pilot Study in a Pig Model. Front Cardiovasc Med. 2021 Oct 25;8:754852. doi: 10.3389/fcvm.2021.754852. PMID: 34760949; PMCID: PMC8572977.

Karami M*, **Mandigers L*,** Miranda DDR, Rietdijk WJR, Binnekade JM, Knijn DCM, Lagrand WK, den Uil CA, Henriques JPS, Vlaar APJ; DUTCH ECLS Study Group. Response letter: In patients with massive pulmonary embolism, we think a combination of VA-ECMO and other therapies should be studied. J Crit Care. 2022 Feb;67:225-226. doi: 10.1016/j.jcrc.2021.11.003. Epub 2021 Nov 15. PMID: 34794835. * contributed equally

Raasveld SJ, Karami M, van den Bergh WM, Oude Lansink-Hartgring A, van der Velde F, Maas JJ, van de Berg P, de Haan M, Lorusso R, Delnoij TSR, Dos Reis Miranda D, **Mandigers**

L, Scholten E, Overmars M, Silvio Taccone F, Brasseur A, Dauwe DF, De Troy E, Hermans G, Meersseman P, Pappalardo F, Fominskiy E, Ivancan V, Bojčić R, de Metz J, van den Bogaard B, Donker DW, Meuwese CL, de Bakker M, Reddi B, de Bruin S, Lagrand WK, Henriques JPS, Broman LM, Vlaar APJ. RBC Transfusion in Venovenous Extracorporeal Membrane Oxygenation: A Multicenter Cohort Study. Crit Care Med. 2022 Feb 1;50(2):224-234. doi: 10.1097/CCM.0000000000005398. PMID: 35100195.